I N D E X

BREAKOUT GROUP DISCUSSION - AVIAN

February 23, 2000

KEYNOTE: "---" Indicates inaudible in transcript.

BREAKOUT GROUP DISCUSSION - AVIAN

(2:02 p.m.)

CHAIRMAN WAGES: All right. We are going to go ahead and get started, if you will. My name is Dennis Wages, and I am the moderator for the Avian Breakout Group. As a moderator, I wanted to kind of lay some ground rules I guess, if you will, and let you all know that my background is not about pre-approval studies, nor experimental models or anything other than the knowledge of the species that we are dealing with.

And hopefully my input would be more in a practical sense when you start looking at comparison of in vitro versus in vivo versus field studies. Plus, I guess we drew straws and I lost, and that is why I am moderator. But I will be giving the summary of this group's information tomorrow at the summary portion of the program.

We are not looking for a consensus, but if consensus points do arise, those will be emphasized in the summary; however, we will try to take all points that are presented and give them in the summary. But again, if I can emphasize certain portions of our program because of consensus, we will be tickled to death.

We have got some technical difficulties going on here. We are going to try to allow about an hour per question. We have got about six hours for the breakout

sessions, and we are going to try, give or take, to spend about an hour per question. Some, it appears, will take longer, and we will modify that, and then hopefully, that will give us about an hour tomorrow to either summarize or, if, in fact, we have other questions that arose during our conversation or dialogue, we will include those.

We are going to keep on track the best we can, and we want to stimulate dialogue the best we can. But I am going to be one to intercept a monopoly on the conversation extremely fast. I want as many people to give their opinions, and we want to stimulate discussion between individuals. But we don't want a filibuster to start, and the moderator will take very straightforward procedures to stop that.

We have a microphone use. We have got a lady that is recording the entire thing. So at first we are going to try with her microphone. She has kind of got a portable microphone that is on her table. Hopefully, just speak loud enough and clear enough and that will be as far as we need to go with microphones.

If it appears she cannot record the information, we have a portable microphone, and we are going to have to probably use this front row to have people speak into it. So try to speak loudly and clearly, and we should be okay.

Jeff Gilbert will be our CVM scribe who will be

putting things on PowerPoint for us, which will be the focus of what I will present in our summary tomorrow. I want to represent you and the group much more than I want to represent me. That is very important to me.

And then, David Grau will be the facilitator from CVM, and I am going to turn it over to him to make a few comments and then we are going to get started on question one. David.

DR. FLYNN: Can I just make a point?

CHAIRMAN WAGES: Yes.

DR. FLYNN: Based on the last session I guess, we wanted to try sort of add some questions to this list, and I think one general question that I think was brought up among a number of people at the panel discussion was the basic objective question in terms of the -- you know, what is the primary objective or objectives of these studies.

So that may be a good starting point, to spend some time talking about that first before moving on to some of the other questions that are there that are a little bit more detailed. I was just kind of giving that message to everyone.

CHAIRMAN WAGES: The objectives of pre-approval studies in general?

DR. FLYNN: Right.

CHAIRMAN WAGES: Okay.

DR. FLYNN: Thank you.

CHAIRMAN WAGES: David?

CO-CHAIRMAN GRAU: My role is just to insure the process that we will be using today. But also, to start off with, are there other questions, time permitting, in addition to the now six that we currently have, that you all would like to address either later this afternoon or tomorrow morning?

So, in addition to the five questions as you see in your agenda and now this initial question about objectives for outcomes on pre-approval studies, what other questions would you like to see this group address? If you don't have them in mind right now, as we go along, please feel free to raise those questions that you think would be important to take a look at.

And what we will do is I will ask Jeff to, please, make note of those questions. And then, hopefully we will make time to address as many of those questions as we can tomorrow morning. So, are there any right now that you can think of that you feel aren't adequately addressed either in the agenda or by this first question?

DR. FEDORKA-CRAY: Excuse me. Other questions? Is that what you are --

CO-CHAIRMAN GRAU: Yes. Other questions that you would like this group to take a look at.

DR. FEDORKA-CRAY: Perhaps I would just raise the -- some of these questions already seem to be, the ones that I would approach, a given model that was already developed. And it would seem that one of the things that we would have to do besides define the objectives would be then to define a model and then to say whether there were positive or negative aspects associated with it.

I mean, one of the first questions was the positive aspects of study concepts presented. You know, there were so many different kinds, you know, hundreds of questions presented and need to be addressed, and there were no -- and there is not a cohesive focus. So, to me then, you would have to not only define objectives, but focus and define some type of model that then we can defend and give the pitfalls and the positive points associated with that.

CO-CHAIRMAN GRAU: So are you suggesting that this group first comes up with a model? Or, after all the discussions, propose a model based on the conversations that ensue over the next five hours?

DR. FEDORKA-CRAY: I guess the way I would look at these -- because some of these also don't seem to fall in the order that I would think would be necessary to define some of the parameters associated with that -- would be to look at objectives and then to define a model and then to list the positive aspects of the model, such as the data gaps, and

then to list a proposed series of steps to achieve the model dynamics. And I think that if that can be done in five hours, that is a tremendous accomplishment.

CHAIRMAN WAGES: But don't you think, Paula, that we need to know the objectives, what we are trying to get at, prior to --

DR. FEDORKA-CRAY: Right. I said the objectives first. So the first thing was objectives.

CHAIRMAN WAGES: And then the most appropriate model that would come close to answering those questions.

DR. FEDORKA-CRAY: Exactly. Yes. I said objectives first.

CHAIRMAN WAGES: I am sorry. I missed that.

CO-CHAIRMAN GRAU: Other thoughts on what was just proposed?

DR. KRUSHINSKIE: My understanding of these questions -- I thought these were just sort of to start the dialogue, but not necessarily to go through, lock-step, through these? Or is that not the --

CHAIRMAN WAGES: These were -- my understanding is they were placed in our agenda to try to cover these. They were CVM's best shot at what they wanted to answer, knowing that it would stimulate other avenues of dialogue.

DR. KRUSHINSKIE: I think Paula's point is well taken, that we don't have a model to discuss.

CHAIRMAN WAGES: I know.

DR. KRUSHINSKIE: We need to do that, and then these are good questions to ask about a particular model. And maybe the idea, when they wrote this up, was that there would be more of a concrete model together by the time it got to this point.

CO-CHAIRMAN GRAU: Right. Something that the group could reflect on during the conversations.

DR. GILBERT: Can I add something to that?

CO-CHAIRMAN GRAU: Yes. Go ahead.

DR. GILBERT: I work in that pre-approval studies working group. Indeed, we are hoping to get input from outside about what is the best model. You know, we are relying on you guys, the experts, to tell us is there a model, Paula, that we could follow. If there is, please, the mike is all yours. We have some ideas in mind, but again, we wanted to get everybody else's opinion on what they would be first.

DR. WEBER: Didn't I hear that perhaps overriding -- at least in the discussion as initially presented -- was the rate and extent of resistance development as a result of the use of the antibiotic in say enteric bacteria? That was one objective that was a starting point for his presentation.

CO-CHAIRMAN GRAU: Right. So that would be one of the objectives. So does that sound like -- going back to

Paula's suggestion, what do you think? Does that sound reasonable?

CHAIRMAN WAGES: So, once we go through the objectives of a pre-approval study, then we would look at the appropriate models that potentially would put us in line to meet those objectives. And then, if and when we get through that, then we could go and answer questions appropriate to specifically a model that we feel comfortable with to answer the objectives.

Is that what I hear you saying? Is that the group's wishes?

VOICE: Yes.

CHAIRMAN WAGES: Okay. Well, we have had one comment already of the primary or a major objective being the rate and extent of resistance development. Do we want to expand on that anymore? Or is that -- that is kind of broad in my estimation, but --

MR. : Dennis, don't we have to include in this, in the objective, what the outcome -- how we are going to use the results from whatever model is set up to make a decision as to whether this drug is approvable or not?

If this is a pre-approval study, then the study, or studies, must be pivotal to the approval of the product. So we have to define what it is we are looking for that will tell us whether a product can be approved or not and under

what conditions.

DR. FEDORKA-CRAY: Yes. I think maybe we are -- I mean, the way I see this is I am almost looking at it as if they are walking in the door -- if you are walking in the door with an application, the first thing you would do is you would look at the compound. The objective would be to define the class of antimicrobial and the potential risk resistance mechanisms that would be associated with it. You know, that we would already know or that we wouldn't know.

DR. KOTARSKI: I agree with Paula. You need to know the spectrum of the activity of the drug and you need to know -- having known that perspective, identify what are the potential resistance mechanisms; of known mechanisms.

DR. MEVIUS: Is that an objective?

DR. FEDORKA-CRAY: To me, that would be objective one.

MR. : My concern is there is questions that would -- we could maybe find answers for that would be nice to know and we should know about the product. But I guess, from an industry standpoint, I want to know what it is that we have to do and what questions we have to answer to get the product approved.

DR. FEDORKA-CRAY: But if you don't go in there, don't you think -- if you go in there with that information right up front to a bunch of reviewers, that that will lay

out the scenario for the thought process? I mean, to me you would want to have it as tight as possible so that you wouldn't leave any room for them to wonder where you were coming from. I don't know.

MR. : Right. I don't know how that helps them make a decision to approve it. That is my point.

DR. MEVIUS: The objective will still be study rate and extent of resistance development. And then, during the process, the first thing you will want to know is what are the mechanisms --- spectrum of what is existing in the field already and then we will go on building the model and study what the effect is.

I think also you should include in the objectives study rate and extent of resistance development of a given dosage, because you are studying at a dosage regiment, and it is not just the product because -- well, when you are talking about dose optimization. If the dosage regiment --- effects on resistance selection. So I think it should be more defined and relate to a dosage.

You are licensing a product in a given dosage for regimen and -- for the specific regimen you want to have a pre-approval study done or a pre-approval study is done.

CHAIRMAN WAGES: Yes, sir.

DR. LUTHER: Lonnie Luther, with the Office of New Animal Drug Evaluation. I have been with the pre-clearance

arm of FDA for 25 years. We traditionally and statutorily been asked by Congress to show safety and effectiveness of a new animal drug product. We have done that primarily in the target animal, with concern for --- indication for use and the dosage; frequency and duration of dose.

But now we come to a new hurdle, and that is the demand of the public to show that antibiotic resistance isn't transferred to other parts of our environment. Primarily to human health care. So our overall riding mandate there is to protect the public health.

So I think one of the first questions you have to ask is what is this new hurdle, and that is why we are here, to discuss what kind of data, pre-clearance, data should CVM ask for on this new animal drug evaluation or ask for for a new poultry antibiotic. And what kinds of information will allay the public health concern.

I don't know if that helps, but I think our objective really here, in terms of antibiotic resistance, is to have at least a defined study that will demonstrate that the public health is not compromised.

CHAIRMAN WAGES: Excuse me. He has his hand up. Go ahead.

DR. WEBER: One of the issues there where this is important -- but also, that after this is learned, is what to do with it, and I think there are further decisions that need

to be made on the management or resistance dealing with it that come after you learn certain aspects. So there are going to be management decisions in terms of post-approval that might come from this information, and that was discussed in the last time.

As far as the amount and the dosage and duration, is it not possible that you might have more resistance develop at some suboptimal dose? In other words, if you go ahead and you kill all the bacteria or you make some effect at the full dose, but if it is suboptimal in some animals or half the dose or someone is not using it, in fact, you may get more resistance development at the dose than you would at the full dose.

So there are issues about what is -- what doses should you study, and I think that was one of the questions. If you study it at the full optimal dose and PD/PD the outcomes, that you might find an actual -- an optimal dose to deal with the resistance development.

If you want to get a handle on -- like Dr. Anguelo said about finding the genes that might be occurring with this, you might wan tot develop that through some other in vitro studies or some sort.

CHAIRMAN WAGES: Yes. Go ahead.

DR. MEVIUS: First I will respond to you. Then I would like to respond to you. I think this should be one of

the purposes --- optimize dosage regimen --- would be in a model --- for the period you are going to look at.

So I think the dosage for it, or the minimum dosages are really the highest and the lowest dosage in the --- should be included.

And to come back to you, I think probably the health issue is an important basis of this discussion. But if you want to have a study done to really get some answers, you need to have years of research with a lot of molecular epidemiology, and the first step in this potential public health research whether there is resistance. Yes or no.

If you can define dosage regimens for --- would minimize the challenge of selection of resistance, and it would also minimize the chance of public health concern. So there is no way of giving a simple model of answering public health concerns, because it is very, very complicated. It depends on the bacteria and the resistant genes and there is a lot of very specialized work ---

DR. GILBERT: Let me just add one point there. Yes. There is no simple way. But is there a way we can proceed with now, knowing that it may take 10 years or whatever? Or a lot of molecular work in the genetics and in vitro and everything. That is going to take a long time.

Our alternative would be probably just to shut down and say no until we figure this out. But we want to proceed.

We don't want to, you know, block development discovery. We have got companies that have products that want to come down the pike. Is there anything that we can start with now and say this is our best guess in February of 2000, as far as what kind of study we can put together to get these drugs through?

DR. MEVIUS: You are asking me?

DR. GILBERT: I am asking everybody.

MR. : I guess, if you look at things that way, where we want to get things going again, then I think you get back to where you have the compounds, you characterize resistance, you look at -- you do these types of things and you beef up your post-monitoring, your NARMS; you beef up your NARMS. You do this kind of information based on what you have determined are the mechanism in those things.

I am not sure you will have all the studies or -- if you go back to dose selection, you know, first of all, I am not sure if you will ever have the study to really -- once something gets out into the market, to really say what is going to happen and get out of the market.

I think you have to understand a compound and know what you are looking for once it gets out on the market, but you really need to beef up NARMS and do those types of things.

CHAIRMAN WAGES: Yes, sir?

DR. WEBER: One of the objectives I thought I heard, and it sounded like a good one, is if you are allowed more than one, is to begin in these studies to collect some information on potential mitigation strategies, like knowledge about the time for the resistance to subside or diminish. Again, that is part of the rate and extent; to see if part of the information on the decline aspect, as well as repetitive dosing.

So I think that -- if that is a broader subset of the rate information, I think that is going to be important in terms of potential downstream mitigation strategies. For example, I believe the -- one of the models being considered now in some of the studies we are seeing is extended dosing and removal from dosing and re-dosing. So there are two or three aspects that are currently being looked at in terms of resistance development and decline.

CHAIRMAN WAGES: But, from a practical standpoint, in poultry, the re-dosing won't be an issue. I can tell you -- count the number of re-dosing that occurs in the field after an antibiotic has been used on very few fingers. So we are getting into a thing that is theoretically great for somebody in the laboratory to look at how resistance occurs, but we are not going to be multiple dosing chickens in the field. So why should that be an integral part of how something gets approved or, you know, a claim put on.

Maybe I am missing something. You are looking at the guys who has got to defend all this.

DR. WEBER: But isn't that a subset that might be useful in other species and not particularly useful here because of what you just said in terms of the dosing regimens you actually use.

DR. KRUSHINSKIE: You also have your judicious use guidelines. The judicious use guidelines of antibiotics addresses the appropriate mechanism of using antibiotics to control resistance issues, as well as retaining the efficacy of those products.

The other question I have -- when you started talking about looking at dosages, that you are going to look for resistance or controlling dosage or dosage, maybe I am not understanding it, but it sounds like one dosage is the dosage that is efficacious against the target organism, period. That is what the products are licensed on.

If I am using batril (sic) to treat E. coli., I want the dosage that treats E. coli. Whether that creates resistance in camplyobacter or not isn't really pertinent to whether that should be licensed for the treatment of E. coli. If that under doses camplyobacter and creates a resistance issue, that is a concern.

But in looking at testing for release, are you going to take every camplyobacter and salmonella glove lot

and determine what the optimum dosage is and control resistance development in each of those species? And then which dosage are you going to license for?

If it is 10 times higher to control resistance in camplyobacter than it takes to treat E. coli., it is not cost effective for me to treat E. coli. with this drug. See what I am saying? Most don't really necessarily go hand in hand.

CHAIRMAN WAGES: Paula, go ahead.

DR. FEDORKA-CRAY: I think that is the crux of the situation here. Maybe you can present it as sort of a main focus and then the subset or the other information that we have to know that helps to provide information for public health.

But I agree. It is the dose that would be indicated for the target pathogen and why look at other doses, if that is what the approval is based on. But, at the same time, I don't think that it would be bad to have other studies going on say, you know, in support of measure and whether -- to understand. And whether that is done by the company or that is done in a research situation where we have other labs or programs supporting it, I think those are different models that you would be talking about looking at different doses, multiple doses, because you are going to get caught in a situation here when you can't get all the parameters looked at in a timely manner to get anything

through.

DR. KRUSHINSKIE: I don't think they are all going to come together to be one --- one uniform dosage.

CHAIRMAN WAGES: And you are really looking -- from a practical side of things, it is more like a therapeutic uses. I am not going to go put my money in the stock of the company that is investigating growth promoting antibiotics to go in food animals. So it is a therapeutic regimen.

The bottom line is, in my mind, and the problem or the questions at hand, is does it, by the therapeutic use of this product effect the potential zoonotic pathogens in their course of exposure during a treatment regimen. Is that not really the bottom line on what we are worried about?

You know, in poultry it is camplyobacter and salmonella as a result of treating E. coli. with a fluoroquinolone. Correct? And so -- pardon me?

DR. MEVIUS: It is not just --- because it is also present of resistant genes in commensal flora that can become --- so it is more complicated.

CHAIRMAN WAGES: Correct. I agree with you. And the potential transfer of that. And then, I guess what boggles my mind is I don't see how we are going to sit here in six hours, versus 25 hours, and establish a study that could answer those questions.

DR. MEVIUS: But if this should be part of the

development of -- whether it is a new drug or a new formulation of an old drug, in the development the company also takes this into account; that the dosage regimen should not only be effective, but also should have the least potential for resistance selection.

For instance, Virginiamycin used for control of posterior enteritis as you presented yesterday. That is therapeutic use or that is mixed in the feed. But also, if it is longer term use, it could very well be the case that strategic use in shorter term at higher dosages would have the same therapeutic effect of posterior enteritis and less effect on resistance selection. So this is the point I am making.

CHAIRMAN WAGES: I understand. But also, you have to look at the big picture of what the pharmaceutical companies are up against. You know, they spend their research dollars right now defending use instead of investigating new use, you know. And to put enough hurdles in front of the pharmaceutical companies, you're looking at all the drugs that is going to be approved for food animals in the United States. And if you don't believe that, I will sell you some land in Florida.

DR. MEVIUS: I think the categorization here in CVM will be very important as -- thinking about which drugs are going to be categorized as category one --- I don't know

really which other drugs will be category one, and maybe the guidelines or the general rules for category two drugs can be quite different.

That is not so really relevant. That is not a direct public health threat. So maybe --

CHAIRMAN WAGES: Well, Virginiamycin is going to go into category one. So they said.

DR. MEVIUS: Certainly. It should, of course.

CO-CHAIRMAN GRAU: Any other objectives?

CHAIRMAN WAGES: How many of what we said are actually objectives? Can we go back and at least look and bullet what we think is objectives.

DR. GILBERT: Yes. Define a model and then defend critique; study the rate and extent of resistance development; decide what we are going to do with the outcome results of those studies; what sort of impact they are going to have. You know, once we find out the bad news or good news, then what do we?

It looks like we need to address the compound first; figure out its spectrum of activity; study something about the mechanisms of the genetics; focus on a dose regimen, which I totally agree with. That is what we have been trying to do. It looks like dosing regimens is an important issue. Beef up NARMS.

DR. FEDORKA-CRAY: I mean, I would say I don't

think those are all objectives.

CHAIRMAN WAGES: Yes. I would just hoping somebody would bullet the objectives so I know what is objectives and what is explanation of objectives.

DR. FEDORKA-CRAY: Can we get a white board in here?

CHAIRMAN WAGES: We talked about that. We wanted a sheet. I don't think we have an access. Should we try? I wouldn't mind bulleting; go back and get the consensus, at least in the group, on what is -- bullet the --

DR. GILBERT: Well, I guess define a model. Would that be number one?

CHAIRMAN WAGES: That would be an objective. I am not convinced we have to one, two and three them. Let's just say --

MS. : The model addresses the objectives.

MS. : Right. You need objectives of what your model is going to follow.

DR. KRUSHINSKIE: If it is to study the rate and extent of resistance development, can we take -- in what? In the target species? Is there any consensus opinion on what it is that we are modeling the rate and extent of resistance development in? Is there more verbiage to that in that guidance document?

CHAIRMAN WAGES: Well, it has been alluded to that

we are interested in the target animals and the commensals, which have the potential for zoonosis, as well as the ones that have the potential transfer, such as the enterococci. I mean, that is a broad stroke of all bacteria.

DR. KRUSHINSKIE: How many species in the gut? I mean, you can't do it. That is what I am saying. There is 400 or some.

CHAIRMAN WAGES: Again, I am just the devil's advocate up here trying to stimulate things. They will keel on E. fecum and fecalus (sic). Probably in the enterococci and a couple of campys and a couple of salmonellas. You know, that may be the keys. I don't know.

DR. FEDORKA-CRAY: Can you say study the rate and extent of resistance development using -- at the indicated dosage in the -- for the target animal pathogen, and then, you can make two define the effect or define the resistance effect? Or define the development of resistance as a result of the indicated use in salmonella, camplyobacter and enterococci?

CHAIRMAN WAGES: Would everybody agree that those at least are the three biggies that we are considered with?

DR. WEBER: You said enterococci. Right? The fact that -- for example, Virginiamycin -- and I am not a microbiologist. But it is now indicated for use in clostridium; for clostridium. What you would say is that

would be a specific indicated organism.

DR. FEDORKA-CRAY: Or that would be the target.

DR. WEBER: But if you had something that was targeted for camplyobacter, would you not look at clostridium? Is that one to consider, in other words, of the five that we have looked at? Or six.

DR. FEDORKA-CRAY: I don't know that I would make that one that I would look at.

DR. GILBERT: Paula, what were your bugs again?

CHAIRMAN WAGES: Salmonella, camplyobacter and enterococci.

MS. : He asked if it should include clostridium. That is what the question was.

DR. MEVIUS: How about --- more general. I think --- make it more general. Food-borne pathogens, like salmonella and camplyobacter.

CHAIRMAN WAGES: But not in poultry though, and we are dealing in poultry.

DR. MEVIUS: All right. And let's say indicator organisms or -- of the commensal --- like E. coli. or enterococci, because you can choose others as well. But, at the moment, E. coli. and enterococci are used.

DR. FEDORKA-CRAY: I think, if you don't define it, Dick, the way things go here, then there is going to be a laundry list of, you know, 12 or 15.

DR. MEVIUS: The problem is, Paula, if you have drugs like, for instance, ---

DR. FEDORKA-CRAY: I agree.

DR. MEVIUS: -- the enterococci to E. coli. So what are you going to study then? So you have to have the concept, and it should be commensal --- which is, by nature, susceptible, and then that could be used as a model bacteria. And, if possible, maybe enterococci and E. coli.

DR. FEDORKA-CRAY: I guess I would just put in there then a qualifier saying limited it to the two top bacteria of concern.

DR. MEVIUS: Right.

DR. FEDORKA-CRAY: Otherwise, you run the risk of -- okay. Well, if we didn't find it here, then let's look there. If we didn't find it there, then let's look here.

DR. GILBERT: Who is the two top?

DR. FEDORKA-CRAY: Just like Dick said, you have to look at the -- what the drug is going to be -- you know, where there is going to be some effect and not something that has inherent resistance to it.

DR. GILBERT: I think Paula hit on something. I mean, this is your opportunity to input. If you want solely to look at salmonella and E. coli., tell me that. You know, is this a good list here?

CHAIRMAN WAGES: Would it be a consensus of the

group to have those organisms as it reads? Or would it be more appropriate -- I wouldn't have it, all those on there. I wouldn't have E. coli. on there.

DR. MEVIUS: It is important.

CHAIRMAN WAGES: Well, for what?

DR. MEVIUS: If you want to have a model study just to study the effect of the use of a drug active --- gram negatives. The problem with salmonella, and also in camplyobacter, is it is not so easy to randomize a sampling strategy. You have a lot of enrichment techniques, of course, and not all animals shedding salmonella. Camplyobacter you have selective plates with antibiotics in there. So E. coli. would be a model bacteria by itself. By nature, --- then you could study in this model the effects of the dosage regimen on the resistance selection.

MR. : Do we know that E. coli. is a good model for salmonella and camplyobacter?

DR. MEVIUS: You are only looking if it is a good model for salmonella. You would also have to -- you would always have to look at the food-borne pathogen, because the direct risk is what is very important. But E. coli. is just -- you can sample it rather. It gives you the best opportunity to objectively determine whether a dose regimen has a negative select -- effect on resistance selection. Just as a model. Whether it can be directly translated for

risk in salmonella in camplyobacter there is a different, --

CHAIRMAN WAGES: Then I am not concerned about it, if it doesn't directly impact the potential for the food-borne pathogen problem. That is what I am worried about, is getting people sick. I am not interested in it.

DR. MEVIUS: But E. coli. is not really different from salmonella. If you have a very clear situation in E. coli, it will also be the case that less -- the more difficult to study and determine in salmonella.

(Simultaneous conversation.)

CHAIRMAN WAGES: Whoa. Hang on. Go ahead.

DR. KOTARSKI: I agree with Dr. Mevius; that E. coli. and salmonella are so alike in their chromosomes that E. coli. is a good --- organism for salmonella, but I have a "but." And that is the exposure of the drugs in chickens. The number of bacteria that are exposed to the drug and places that they are exposed to the drug may be different than salmonella.

So, from that standpoint, the drug distribution and the drug/bug interaction for E. coli. may not necessarily be a good model. So maybe we could think about -- you know, advise the CVM to think about the most appropriate organisms in context of the spectrum of activity and the drug distribution. We are looking at the top two of the most important organisms. In other words, you have a depend

clause in there.

CHAIRMAN WAGES: Let's just stop right now and let's just look at -- with those four up there, let me have a show of hands. Who wants to see that number two stay as it is with those four organisms represented. Raise your hands.

(Show of hands.)

CHAIRMAN WAGES: Okay. And the ones that want to see, I guess, E. coli. taken off of there and have those three organisms?

(Show of hands.)

CHAIRMAN WAGES: Okay. So we don't like any of those. What is the alternative? Now, Paula. Go ahead.

DR. FEDORKA-CRAY: Thanks, Dennis. How about if you say indicated use in food-borne pathogens, such as salmonella and camplyobacter or those designated as most important for that -- at that moment in time? Or those designated most important, in addition to commensal pathogens. Or commensal bacteria, limited to the two top as indicated? Like Sue says, for bug/drug interaction, such as E. coli. and enterococci. You know, that puts all your qualifiers in it.

DR. MEVIUS: We have to keep in mind that E. coli. is not just model bacteria. We include enterococci as a potential carrier of resistant genes transferring genes to other populations. E. coli. is also a population carrier --

potential carrier of resistant genes transferring through zoonotic bacteria or through pathogenic bacteria. So that is a second reason why I think E. coli. should be included.

It is the same sort of information as the enterococci. Enterococci by themselves are not zoonotic. It is the potential carrier of genes --- case for E. coli.

Always the food-borne pathogens is relevant, if the drug has a gram negative spectrum, otherwise, include one of the two indicator organisms or whatever you want to call that.

DR. GILBERT: If one or the two were both there for all time, could that be a standard, you know, that we could apply even handedly to everybody and not worry about it over time? Ten years from now if we said, oh, look at the guideline and do salmonella or E. coli., would that be sufficient? Would you be satisfied? Or would the public be satisfied knowing that the studies were done in those organisms? Or, is it the bug du joir?

DR. WEBER: Could one look at the spectrum of activity that you develop when you -- to see where important inhibitions might lie? I am just throwing it out.

(Pause.)

CHAIRMAN WAGES: So, do we need to complete this number two more?

DR. FEDORKA-CRAY: Would it be food-borne

pathogens, such as salmonella and camplyobacter.

DR. GILBERT: And take out E. coli.?

CHAIRMAN WAGES: Or E. coli. or and E. coli.?

DR. FEDORKA-CRAY: No. Salmonella and camplyobacter and commensal bacteria.

CHAIRMAN WAGES: Take out E. coli.?

DR. FEDORKA-CRAY: No. And commensal bacteria, such as E. coli. or enterococcus. Or two of the most important bacteria indicated at the above bug/drug combination.

MR. : But shouldn't it -- I could be terribly off base on this. To me, I think this is a lot of stuff that would be great to know in looking at these two things. But still, shouldn't we be choosing the bugs based on the risk to human health?

If we look and we say we are going to choose camplyobacter, shouldn't that be chosen based on -- you know, if you are going to choose which ones you are doing, shouldn't it be chosen based on the risk to the public? You have to work that in somehow. I mean, there has got to be a reason why you investigate it. It has to be based on a risk, if you come up and say you are going to protect human health. I just throw that out.

But, if you look at the risk assessment of it actually happening and --

DR. WEBER: That comes later.

DR. MEVIUS: That comes with the probability of the real risk, which is, we know, very, very low.

MR. : Then you generated all of this information that is nice to have and nice to know and you find out later down the road that the risk was negligible? It is very complicated. I just throw that out about, you know, you do all this and then you say, okay, here is all this information. But, in the overall scheme of things, how do we relate it to the risk?

DR. FEDORKA-CRAY: That is the whole thing that everything is -- that is the million dollar question. Why are we doing this whole thing?

MR. : You know, through every stage you have to keep asking yourself.

DR. MEVIUS: That is why --- categorizing also groups of antimicrobials. Which are the most important ones and which are -- for which it is not important when you show selection of resistance. If you have selection of resistance --- and salmonella, then that can be very important, but --- so the categorization has to be included. That is very important.

DR. KRUSHINSKIE: I agree with that. Really, it is going to be an exercise in spending a lot of money and time if it is not a significant drug for human medicine. It is a

bacitracin ---

(Simultaneous conversation.)

CHAIRMAN WAGES: Excuse me. No. Hold it.

DR. KRUSHINSKIE: --- a big use in human medicine. I can see, for the category one drugs, it is very important.

CHAIRMAN WAGES: Okay. Richard, go ahead.

DR. CARNIVALE: You mentioned before you thought this was related primarily to therapeutic.

CHAIRMAN WAGES: Correct.

DR. CARNIVALE: I guess I am a little confused then why we are talking about enterococcus and maybe commensal bacteria, because I had an understanding that CVM had never really had a concern about therapeutic antibiotics really affecting commensal organisms to any great degree. I guess I thought that issue was mainly related to the continuous feed additive type.

CHAIRMAN WAGES: But I think what we are doing is -- in my mind, is this the potential for any pre-approval drug that might have a gram positive spectrum? If somebody came out with an oralseptive (sic) that was going to go into the system, we would have to have enterococci. That would be a bigger player now. Right?

DR. CARNIVALE: Even for therapeutic.

CHAIRMAN WAGES: Yes. Wouldn't it?

DR. CARNIVALE: Well, I am asking the question. I

guess I just --

CHAIRMAN WAGES: I mean, because it is gram positive. I guess i looked at this as global. I know we are shooting down the fluoroquinolone therapeutic avenue. This is probably a joke, but this is a pre-approval for potentially any antibiotic, which will never happen in poultry, but we are going to do this anyway.

MS. : But is the pre-approval process for every category, drugs that go in any category?

CHAIRMAN WAGES: I would think it would be. And I don't know the answer to that. I would ask CVM. But, to me, it would be modified. I mean, if you are looking at a category three drug, you know, I think you are looking at -- these studies would be not as severe as something that was potentially a two or a one drug.

DR. GILBERT: They may not be required at all. If it a low -- you know, never going to be used in humans and low, potentially you could make the case that it be waived.

CHAIRMAN WAGES: Go ahead.

MS. : I am just reading from Dr. Flynn's first summary statement on pre-approval study objectives. He does state resistance -- pre-approval study objectives. Resistance, how rapidly does decrease susceptibility emerge rate, which is what is the magnitude --- susceptibility --- zoonotic pathogens in the animal's intestine tract.

The third relative point is germane to what we have to use in every case. This is not all uses. Classes of drugs will require most resistance --- pathogen load studies. The second bullet on this issue. "Certain uses and classes may not require pre-approval studies," and that relates to the category one, two, three high/low ---

CHAIRMAN WAGES: Okay. That would be my understanding.

MS. : So what we are tailoring here though is for category one. Is that what --

CHAIRMAN WAGES: Well, I think that is where the most potential for concern is.

MS. : Can we limit this to category one?

CHAIRMAN WAGES: We can do anything we want to.

DR. WEBER: To what extent is the resistance development an issue with the longevity of the drug use itself no matter what class? I mean, you know, as far as its efficacy. Actually, I think we will shed some light about potential longevity of the drug. At least at the doses suggested.

CHAIRMAN WAGES: Well, I don't think it matters. When has a drug every been pulled off, except for the old neomycin and terramycin (sic) because they didn't work? They are still there. Neomycin and terramycin in most E. coli in broilers don't work, but they are still out there with claim

on it.

DR. WEBER: --- using them ---

CHAIRMAN WAGES: Too expensive. No. It is too expensive to use them.

DR. KRUSHINSKIE: But it is also behooves the drug company to understand how rapidly resistance develops to their product for the target organism because why would you spend "x" number of dollars to develop the product if it is going to be -- would lose its efficacy in six months?

CHAIRMAN WAGES: Is that something they would do though normally? Or should it be required in a pre-approval study? Yes. They are going to do it anyway.

MS. : But that information ---

(Simultaneous conversation.)

MS. : I have a question. If we approve a drug for --- bacteria, --- as indicated ---

CHAIRMAN WAGES: Pardon me? You have to repeat that, please.

MS. : Okay. If we approve a drug against --- positive bacteria, then we use all those gram negative bacteria as an indicator --

CHAIRMAN WAGES: Your target organism would change, number one, if you were dealing with gram positives. Correct?

MS. : Yes.

DR. MEVIUS: You have to relate to the spectrum of your specific antibiotic, otherwise it shouldn't test irrelevant.

CO-CHAIRMAN GRAU: How are we doing? How are we doing? I just want to check in with you and see because we are about an hour into it and --

CHAIRMAN WAGES: I am totally confused.

CO-CHAIRMAN GRAU: Right. One of the things I am thinking of is the need to scope this, which is really the nature of the conversation. Scoping. How broad? How narrow? What do you want to focus on? Can you have one study model for everything? And, if not, which one/ones would be most impactful, relevant, desirable to look at over the next, now, five hours? We started at six.

So, you guys are -- again, not to rub it in -- the experts, and I certainly am not. That is why I am checking in and asking how you would proceed at this point, being that the ultimate objective of our session has now become to come up with a suggested study model. How are we doing?

CHAIRMAN WAGES: Yes, sir?

MR. : I would say go back to what is being referred to here, which is the framework document, as it exists, to eliminate the necessity of describing concepts, and the questions here do not relate to models. They relate to concepts, study concepts. You have a class three -- a

category three drug, which is --- potential. You probably are not going to have a pre-approval study. So we don't need a study concept. Get rid of the stuff that you don't need to talk about here and then get into the stuff you do need.

CHAIRMAN WAGES: I can't answer your first question. We are not breaking until 3:30. That is the only thing I can tell you.

DR. KOTARSKI: Well, if we focus on defining objectives and then a first stab at a model for category one drugs, we can always build onto it for the lower categories.

CHAIRMAN WAGES: Dennis? You have that look. You're thinking.

DR. COPELAND: It seems to me we still have to come to grips, first, with what we are going to do with whatever we come up with. What is the objective as far as the approval process is concerned? Where does it fit in? How is that going to help us make a decision on what to do with that drug? If we don't know that, then I don't know how we can design a model where it is going to --

CHAIRMAN WAGES: Is the pre-approval studies an avenue to categorize the drug into one, two or three? Okay?

MR. : No.

CHAIRMAN WAGES: Why not? No. Seriously. If we use pre-approval studies to identify the mechanism of resistance, the potential cross resistance occurring in human

drugs, et cetera, why isn't that study an objective to help characterize or categorize that drug in the framework document? That has been bugging me all day.

And I don't see why those pre-approval studies would not have an objective to do that. Okay. That is all I know about it.

MR. KOTARSKI: My understanding --- the category one, two and three are an identification of the --- so they drive the level of testing that needs to safely approve that drug. So therefore, if it is a category one, it means that it is an essential drug in human medicine; and therefore, if a sponsor wants to go forward with that particular drugs -- we will say it is --- I want to take --- and I want to put it into the animal population.

If I do so, I better have strong reasons to say that that is not going to have an impact on resistance emergence in human health. I have to do all those studies to do that, whatever they might be. But the studies mitigate whether or not you can go forward.

CHAIRMAN WAGES: Claire, you are smiling. Is that good? No?

DR. LATHERS: That is not it. We are listening.

CHAIRMAN WAGES: Yes. But we need a little input on some perspective at least. We will tell you if we don't buy it.

DR. LATHERS: Okay. I think, in terms of categorization, the question is do you categorize them and then do your studies? Or do you do the studies and use that to determine the categories? Is that what you asked?

CHAIRMAN WAGES: That is what I asked.

DR. LATHERS: Clearly, the framework document is telling us that category one are drugs that are essential to human use and not necessarily going to be duplicated --- so we need to protect them. So now you are back to that initial question that you kind of brushed off that someone asked earlier about what is the relevance to public health. Human health. And here we are.

We are balancing this overall public health need with the animal need, which brings you back to the question is it therapeutic needs in terms of animals or in terms of antibiotic --- so it is not an easy answer. You have to decide, as a group, what you think is the best type of protocol that you might -- and I think what I am hearing is that it may change, depending on what you are looking at.

CHAIRMAN WAGES: Paula had her hand up. She is falling off back there.

DR. FEDORKA-CRAY: Now I am getting confused, because I don't think that -- I think that you would have to know what the category is, the potential category is, from the get-go.

If it is a class of drug -- if it is a fluoroquinolone, I think you have a pretty good idea where that is going to fall as far as a category goes, because you can't do enough of studies to -- well, let me put it this way. I think you can design all kinds of studies to give you the answers that you want. Then, depending on where you would want to classify it, that that might not satisfy -- that may not be rigorous enough.

Or someone else might say, well, if you did it this way, then we know that you would probably get this, and so, do this to make sure that you -- you know, you get yourself caught into it and you have to 500 permutations. So I think that you know already whether it is a category. I think we have to go from the idea that we know what it is.

DR. LATHERS: All right. So Paula's suggestion is that we start with the categorization.

DR. FEDORKA-CRAY: And this would be a category one.

DR. KRUSHINSKIE: But some of them, like Virginiamycin, is not a direct human drug, and that is where the conflict stems.

(Simultaneous conversation.)

CO-CHAIRMAN GRAU: Let me just -- can I --

DR. KRUSHINSKIE: But --- itself is not. So now it is a tier three drug that is actually ---

(Simultaneous conversation.)

CHAIRMAN WAGES: Okay. We have to -- the facilitator has got some input and then I want to ask Mike to go ahead.

CO-CHAIRMAN GRAU: I just had a question. Is there a distinction between the premises one makes, the criteria that one uses for the study itself and then there is the study model? And the question is what do you want to focus on during these discussions? Because we are doing both.

And I am not saying it is not necessary. I am just saying that there are two things out here. Is it to address the model? Is it to address the criteria or the premises behind the development of a model or use of a certain model? Is it both?

MR. : It has got to be the latter.

CO-CHAIRMAN GRAU: Okay. Whatever you all -- you know, do you want to say what you are thinking?

MR. : No. I think you have to address the premises on the model.

CHAIRMAN WAGES: Mike, go ahead.

MR. : Thanks, Dennis. I was just going to clarify. In my mind, as a sponsor, I think what I heard now --- we pretty well have an idea of what category we are going to fall in when you start off. Because, if we don't, if we are going to follow the path of, well, we will do some

studies and then we will figure it out, it is too late.

What I hear the assumption is is that for the exercise we are in right now is let's assume we can categorize from the start. So the sponsor and the center would sit down, at the very beginning of a project, and say, well, we believe this falls into say a category one, and so therefore, as a sponsor, I go away and I have a pretty good idea of what I am going to have to do.

One piece of that, in poultry, would be whatever we design here. So I just wanted to clarify, in my mind, where I thought we were going.

CHAIRMAN WAGES: That is where I think we are going, but I am not going to guarantee anything at this point in my life.

DR. WEBER: What I think I heard Bill saying is that while we haven't had a statement about the framework document and the categories, I think I heard him say that they might not -- studies may not be required for a category two. But let's assume, at least for this discussion, that this work will be required for category one and category two and to what extent.

You know, whether or not you include the -- if category one throws out the feed use drugs or not. You know, that apparently is part of that discussion in terms of the policy development. And I agree with David; bringing us back

to the focus.

If you are in category one or two and you need to do resistance work, --

CO-CHAIRMAN GRAU: What do you do?

CHAIRMAN WAGES: What are you going to do?

DR. WEBER: Now you are looking at the objectives. Should we look at the appropriateness of the model?

CO-CHAIRMAN: Right. So you might want to start off of what you all were saying, which is category one, category two as a premise. So what should be included in a pre-approval study to indicate what you have up there.

DR. KRUSHINSKIE: Could I make a suggestion for modifying objective one? Study the rate and extent of resistance development in selective micro flora in the target animal, poultry. The second one addresses food-borne pathogens and commensals. Would not the first to be to look at the resistance development in the target pathogen?

CHAIRMAN WAGES: Target pathogen. Yes.

DR. KRUSHINSKIE: Or is that just assumed to be done?

CHAIRMAN WAGES: No. I think that should be done.

DR. KRUSHINSKIE: Because those two are redundant the way they are. First it states it at one and then it restates it at two.

CHAIRMAN WAGES: Target pathogen or the target

animal. Just take out target animal. Put poultry. We are in poultry. That is the only thing I am convinced of. We are in poultry.

(Laughter.)

DR. KRUSHINSKIE: And then number two is the food-borne pathogen commensals.

CHAIRMAN WAGES: Okay. Sir?

DR. MEVIUS: Nobody is really happy with the pathogen level studies, but --- objectives --- think it should be in the objectives or not? You have to deal with it. Or is that up to us?

DR. GILBERT: Yes. I mean, pathogen load is an important question. When you put the drug on there, is it going to cause the animal to shed? Like the 558-15 studies were originally intended to look at. I think Jean Cooper probably told you something about our history on that. So pathogen load is an objective. Is it an important objective? Is that what the experts say?

CHAIRMAN WAGES: Well, we have heard both yes and no in the previous -- yesterday and today.

DR. MEVIUS: The rate and extent of resistance development. Something else --- general conclusions --- yesterday was that the studies are so -- you can vary the studies; that it is very difficult to conclude something from that. Maybe we can make a short conclusion that this is not

something to focus on.

DR. GILBERT: Pathogen load.

MS. : Is it all those pathogens or the target pathogens?

DR. FEDORKA-CRAY: It doesn't matter if you don't have resistance developing in -- I mean, the idea isn't --

DR. GILBERT: If there was no resistance developing in the resident salmonella, but, all of a sudden, the birds were shedding it like a fiend, that would be a bridge we would have to cross. And I don't know the history of the all 558.15 studies and where each one of the drugs that we all know about went through there and what the impact was. If it increased the pathogen shedding a lot, problems.

DR. FEDORKA-CRAY: But, Jeff, in a way that is like double jeopardy, because you are talking about a resistance issue. And then you are saying, well, there is not a resistance issue, but there is a pathogen load issue, and it seems like that should almost be a separate concern.

DR. GILBERT: We actually had originally set this up to do a couple of days of resistance and a day of pathogen load, and I think the way it got whittled down is pathogen load got sort of shoved to the back for right now. But that may be the subject of another workshop in the future. I don't know.

DR. FEDORKA-CRAY: So what happens if you don't

have resistance, but you have pathogen load? And what happens if you have pathogen load at two logs, but you don't have pathogen load -- you know, if you have pathogen load at one log, but you only have a two-log reduction. I mean, we don't know what pathogens.

We don't know how pathogen load impacts human health outcomes. There is no information to say how that impacts human health outcomes.

DR. GILBERT: So we should not assume that just because the birds are shedding with salmonella it is going to have any impact at all?

DR. FEDORKA-CRAY: I think that we don't know how. That is right, because I don't think that we can define the impact on human health at this time to say that -- you can't design enough of those studies in this model to cover both of those. Those are two entirely separate questions. You can't do that.

MR. : Does it affect transfer between --

CHAIRMAN WAGES: Pathogen load? Is that what you are talking about?

DR. FEDORKA-CRAY: No. I mean, any time you have more bugs in the environment you are going to have a greater risk of exposure. But if they are not resistant bacteria, you know, -- I mean, you can't design the study to say, okay, you are either going to have to look at one or the other

really.

Now, you will have some idea of what the drug is doing, and those are the types of pieces of information, I think, that you can use to build other studies that you might want to use to support say continued use of the drug. Or you might have someone come back and say, well, can you treat the dose so that you can increase or decrease the pathogen load a little bit.

But if we know that in the program now we have very little coming out on carcasses, and we -- and I can tell you that, you know, when you have clinical disease occurring, especially salmonella, immediately, within 24 to 48 hours, you have anywhere between five and six logs per gram of feces being shed in the environment, which then goes down to, you know, very low negligible levels for weeks on end.

So you can't -- that is -- I don't think that is a relevant issue at this point in time, because there is nothing to support that at the slaughter end right now. There is nothing at all to support that. Zero.

CHAIRMAN WAGES: So what statement do we want to make about pathogen load? Right now it is a separate issue. It is not relevant in the pre-approval study for the resistance issue?

DR. FEDORKA-CRAY: It is not relevant for the pre-approval.

CHAIRMAN WAGES: Put that down.

(Laughter.)

DR. FEDORKA-CRAY: I think let USDA worry about that.

CHAIRMAN WAGES: Put that down.

DR. GILBERT: That is Paula, P-a-u-l-a?

DR. FEDORKA-CRAY: Send money from Washington down. No. Don't put that there.

(Laughter.)

DR. GILBERT: You shouldn't have said it, Paula.

CHAIRMAN WAGES: Paula, can I have your cards so I can pass them out to the people?

DR. FEDORKA-CRAY: Dennis, I am on so many lists now it doesn't matter.

DR. GILBERT: Are you soliciting for more work, Paula?

CHAIRMAN WAGES: We are not doing too bad, because we have already listed the pathogens to be focused on in pre-approval study, which was one of the questions. We have answered a good question.

And now, considering the pathogen load, and one of the questions was factors considered when you are trying to model pathogen load. We have pretty much put that to rest. But one area that we might jump to is what are all the considerations when modeling for the development of

resistance.

That is one of the questions that was actually incorporated with the pathogen load. What factors should we consider when trying to model resistance development? Are there any thoughts on that?

Well, it is 3:15. If that is a good stop, let's go ahead stop for 15 minutes.

DR. KOTARSKI: One comment on the objective pathogen load is a separate issue. Until a link can be made to human food safety or human health safety? A link to what?

DR. MEVIUS: (Away from mike.)

DR. GILBERT: What was that?

(Simultaneous conversation.)

CHAIRMAN WAGES: Do you want to take a 15-minute break now and let's say in another hour 15 minutes instead of a big 30 minute one? So let's be back here at about just a little bit after -- 3:35 to be back, please.

(Whereupon, a brief recess was taken.)

CHAIRMAN WAGES: Okay. We are going to go ahead and get started. We basically answered one of the questions concerning pathogen load, and basically, we have come to the conclusion that it is not appropriate to be considered in pre-approval studies, and that is what we will convey tomorrow.

MR. : So it is really not separate then? It

is just pathogen load not relevant in pre-approval. Right?

CHAIRMAN WAGES: Well, and then process it separate. Or do you want separate out of there?

MR. : Yes.

CHAIRMAN WAGES: Why don't you want it in there?

MR. : Because, if you say it is not relevant in the pre-approval process, it is not relevant in -- I just don't think we need to say separate. I mean, for the record, we don't want to get -- we don't want to have to rehash this later, do we? So it is not something we want to discuss separately. It is just not relevant.

CHAIRMAN WAGES: My impression is we have a consensus around here.

(Simultaneous conversation.)

CHAIRMAN WAGES: Whoa. We all can't talk at the same time. It doesn't work. Not in my playhouse.

I thought it was the consensus of the group that pathogen load was not relevant to the pre-approval process, period, and that it is not -- we are not going to consider it in this process, period. End of report. Is that not the consensus of the group?

MR. : The point I wanted to make is if you say that, you might want to say why. That is all.

MS. : On the other side you could say somebody should have to tell us why it is relevant. Why

should we have to defend that it is not relevant? Why does CVM think that it is relevant to pre -- with resistance?

DR. GILBERT: Statutorily it is in the regs right now, 558.15. It is on the books. Why or why not we don't care. It is in the law.

CHAIRMAN WAGES: Is that for therapeutics? No. That is for growth promotants. Correct? Maybe we need to go up in the first part of this and say, look, we are talking about therapeutic antibiotics here.

DR. GILBERT: Therapeutics only.

CHAIRMAN WAGES: Okay? So, maybe back up here in the front we need to start tomorrow and say, look, we are looking at therapeutic interventions here and not growth promotants, because the pathogen load concept, with what maybe you are talking about and what was just related to me is growth promotants. Is that not correct?

MR. : Can we restrict this to just therapeutics? Or isn't this supposed to cover both? I mean, I recognize, in reality, you are probably not going to see anymore growth promotants in poultry, but

DR. MEVIUS: I think you should not restrict, but the presentations have shown that pathogen load studies have so many restrictions it is very difficult to do any conclusions. The conclusion that was drawn is actually valid; that we shouldn't focus the attention on it. I would

suggest not just to focus on therapeutics.

CHAIRMAN WAGES: I would probably agreeing with that in thinking and not restrict it. Then, do we need to qualify the pathogen load statement? I mean, I don't have a problem saying it is irrelevant. Next question. We will go on about our business.

DR. CARNIVALE: I think the document could apply to both, because there may be drugs that are proposed in the feed for control of disease, for example. Not necessarily growth promoters, but are longer term treatments. That is possible.

The other issue is we are not writing a regulatory document. I mean, we are writing a scientific document. So it doesn't matter what the regulations currently say. We are talking about this from a scientific standpoint.

CHAIRMAN WAGES: Okay.

DR. GILBERT: I am going to take this out.

CHAIRMAN WAGES: Yes. Then take the top out.

DR. GILBERT: And do you think we need some clarification down there on the pathogen load?

CHAIRMAN WAGES: I think we will leave it like it says, unless somebody says different, and I think the consensus is to leave it like it is read. It is not relevant. And if they want to take out separate, I don't have a problem. Just put "pathogen - not relevant, pre-

approval process." Call Paula at the USDA.

DR. FEDORKA-CRAY: I heard that.

(Laughter.)

CHAIRMAN WAGES: Okay. Involved in that question, considering the pathogen load. If we are looking at a model situation, what are the factors to consider in resistance development? How would our model -- how would you put the model together to -- well, the question specifically reads, "What factors should be considered when modeling resistance development," period. We are not going to include pathogen load. So, any thoughts on -- in our model what should be considered?

DR. MEVIUS: To mimic the field situation is a suggestion.

CHAIRMAN WAGES: I am a big proponent of that, because I think that is the real world. Hard to do. You know, difficult. Well, no. I think the question that we need to discuss maybe is in the field situation it is difficult to reproduce and validate that, and is that a big deal?

You know, if you mimic field situations, from a practitioners standpoint, a poultry veterinarian, you can't mimic that consistently. You can't mimic the percent moisture in the litter consistently, which will effect the number of bacteria that stay in the litter that is re-picked

up. You can't mimic x, y and z. Does that matter? Which means you can't validate it in the field.

DR. MEVIUS: You could also do it in the field, but then you will add a lot of variables, as was said by Paula in her talk. So at least you would have a model approach. Yes? And then post-approval studies would show whether in the field eventually something else would happen.

CHAIRMAN WAGES: Would comparing in vivo type of experimental type models looking at resistance in the development -- this is a question I have got. Could our models be established to be predictive and could we have an adequate comparison between an in vivo experimental model?

And let's say the resistance exacerbates twofold or threefold or decreases in the field situation. How would those be weighed in the pre-approval process? Or does it matter?

DR. MEVIUS: I think in the pre-approval process you wouldn't have information about decreasing or increasing resistance in the field situation. You are doing a model study to predict something, and we know, because of events that can occur, you would have to -- something to follow-up; do some follow-up.

MR. RUPP: So, when you say predict, does that mean that you are generating data that would give us an insight to the variable in a risk assessment? I mean, if you are going

to predict something and you are going to predict the resistance, actually a happening, don't you have to take in -- we are talking -- you know, I keep coming back to the human food safety issue.

I mean, is the model supposed to give scientific data for input into the risk assessment? I don't know. I just throw that out there.

CHAIRMAN WAGES: Well, we are back to the original question. What is the purpose of the model?

MR. RUPP: Well, no. But I think you need to know. I mean, that is one thing. Those variables are -- you need to define those. What you want to get out of it. Right?

DR. MEVIUS: Right.

DR. WEBER: I thought we defined that earlier, the rate and extent of resistance development.

MR. : That is basically it.

(Simultaneous conversation.)

MR. : What do we do with that information?

DR. WEBER: We are going to put into decision elements and management decisions about how the pre and primarily post-approval activities will unfold. We haven't gotten into that. We haven't published that aspect of the framework, and we are not here to try to defend or project how that is all going to be done, because that hasn't been completely developed.

MR. : See, that is where I am really struggling with this thing.

DR. WEBER: A lot of people are apparently.

MR. : How are we going to design studies to show resistance development and not know what we are going to do with that data when we have it developed; how it is going to be used?

If it is going to be used for post-approval monitoring efforts, then why don't we just put all of our effort in the post-approval monitoring, because we know resistance is going to develop. Does it really make a lot of difference whether it takes five years or 10 years, as far as -- I just don't understand what the pre-approval study is going to do to help you make the decision as far as the approval process is concerned.

CHAIRMAN WAGES: I need to make a housekeeping statement real quick. For those of you on this side over here that are not very loud, you are going to be asked to go to the microphone or get it passed to you to speak up, because our person in the back is having trouble hearing some of the people that don't have the voice to carry so she can pick it up. So, just be aware. Either speak up louder or grab the mike. Thank you. Go ahead.

DR. LATHERS: One question that we could ask is in terms of the pre-approval studies, are they going to be part

of a qualitative risk assessment. I think that is what you are asking and what you are suggesting. I don't know if you meant quantitative risk assessment or qualitative.

MR. RUPP: When you look at what we have done already on the risk assessment and the different variables in there, I think every single time that you are doing this you still need to look at that overall. I mean, just because you have resistance development, just because it has this, if it develops very quickly, but we don't take into effect that it gets to the slaughter house and it comes out the other side with nothing, then what is the risk to human health?

I guess I always thought that these pre-approval studies were supposed to give us more of a scientific insight into better defining and -- you know, to lower the probability and make the field more confident about the assumptions and those types of things that we put into that risk assessment.

DR. LATHERS: Jeff, I don't think you have added his last thought.

(Pause.)

DR. KOTARSKI: My interpretation of what you just said is should the study have as is an objective to be used in a risk assessment of some sort. Is that what you are saying?

MR. RUPP: I guess I am with Cope. Let's do this

stuff, but let's make sure that, number one, we are looking to see what the human health impact is. That is why we are all here. That is why we are doing this whole thing.

If somebody decided that we are in quandary, that something is wrong right now, we need to know how much we are affecting human health.

DR. KOTARSKI: That is what I meant by risk assessment.

DR. WEBER: Do I interpret that to mean then that you would like to evaluate -- besides perhaps the resistance profile that the drug may generate in a bug so you can actually find it after the approval. But are you suggesting then to help with a potential risk assessment downstream perhaps we should consider issues such as the prevalence of the resistance in animal populations, as well as in the human, before approval so you can monitor it post-approval?

And, in the process, be working on mitigation strategies about how you can lower -- and some of these studies are already designed, I guess, to look at return to baseline and other issues involving dosing and regimens like that.

MR. : It seems to me like good baseline data is pretty important to have for a surveillance program.

DR. WEBER: In humans and animals?

MR. : I would think so. You know, the NARMS

program is a good start. I think it really needs to be beefed up. You know, build on that.

CHAIRMAN WAGES: How are you doing, Jeff? Are you catching the drift?

So we have a segment here that doesn't understand how this pre-approval study data and results are to be used for either an advantage or a disadvantage of the approval process. Go ahead.

MR. : I thought it was good what Lonnie pointed out. From the regulatory standpoint, what CVM needs, and that is some assurance that we are not going to cause other health problems. Can't that be addressed with a surveillance program. You have a surveillance program in place, you have your judicious use principles and these sorts of things.

Do you really need this pre-approval study? What does that really add to assuring public health? I mean, if it does, fine. But I guess I am struggling to see how that does and how that enters into the approval process.

DR. LUTHER: I will just stand so you can hear me. I think that is an excellent question, and I don't know if we are on the right course. I can say that political pressures are real, and Dr. Sundlof can testify to that. All of you can.

You know, we don't have particularly specific

language in the statute that says go do this or that. You know, we are generally charged with protecting the public health, and we have our cousins on the human side that think -- some of them think that they would be fine if we didn't use antibiotics in animals at all.

That is a bit of a naive view of the world. So what is our role in the pre-clearance area? We are pressed to the wall. We needed something to say to the world that if we approve the product -- we have to answer to our congressman and the consumer groups. You know, we lack something in our arsenal to say we made the right decision. So how do we answer to the public? How do you answer to the public that placing a new antimicrobial in the marketplace for poultry is a safe thing to do?

To me, that is the objective and just how we answer that I am not certain. But I do think that post-approval monitoring is an option. A good option. You have done that with one of your products. So maybe you can speak to that better than I.

DR. COPELAND: I think the verdict is still out. But it seemed to me --- I don't hear CDC saying you need pre-approval studies to demonstrate that your product is safe. What I am hearing them say is you need a surveillance system and a way to get --

CHAIRMAN WAGES: Dennis, she can't hear you.

THE REPORTER: No. It's your pen.

(Laughter.)

CHAIRMAN WAGES: Excuse me.

DR. COPELAND: What I hear them saying is we need mitigation steps when we see resistance becoming a problem.

DR. LUTHER: I just want to say that the people that have made our pre-clearance decisions in the therapeutic area really aren't here unfortunately, and most of those on the cattle side too are probably over in the cattle group. So I don't have the direct experience and the background knowledge of why we started down this pre-clearance requirement route, but it was Dr. Sundlof's choice I think to require some information.

And I don't know exactly what was required, but -- and it is in an area -- you know, a fiery furnace so to speak.

CHAIRMAN WAGES: Okay. One more comment and then we need to get back and focused.

DR. WEBER: I think what I heard Dr. Anguelo mention is that he saw this as an opportunity to collect data and information, both in vitro and in vivo. Not only on the mutation rate in bacteria, which could be in vitro or -- and balance that against what you see in vivo. He mentioned the need for field studies, the resistance gene in normal bacteria. Actually what is out there to begin with.

Also, optimal dosing rates to minimize resistance. In other words, the PK/PD stuff so that when and if problem arises, you don't want to wait for five years, when it jumps up and bites you, to say how do we address this. So I got the sense that he felt it would be good to get this kind of information up front. Also, to get the fingerprint of potential resistance genes so we can look for them as they might develop.

And also, the issue of transfer. That might be useful later on. So I think he -- I sense that he felt that the pre-approval requirements in this area would be good for the agency to collect the information so we will have it at hand as we start down the monitoring aspects post-approval. Both in NARMS and the CDC, hospital -- you know, the human side as well as the animal side.

I think that both sides are going to be important, and I think you are going to see those surveillance tools hopefully increase even more as we go forward.

MR. : To me, those are data that needs to be collected, but they are not pivotal to the approval of the product. In other words, you don't make a decision based on that data. It is data -- it is like baseline susceptibility data. Obviously you need to collect that before you start selling the drug.

DR. WEBER: There may very well be the need for

true baseline data. So later on, when and if we have this discussion about thresholds or non-thresholds, but action activities, you know, the potential for increasing activity prior to withdraw -- and I like the idea that Cedar has. Opportunities to do something other than withdraw as they interact and get that information of their subpart H in 314.

There is an opportunity for that interaction to monitor, as well as rachet up the surveillance when it needs action, short of withdraw. I think it is important for us to use the pre-approval side to get the minimum information that we need to deal with these activities, both in baseline data and information that we might possibly use in mitigations and other activities down the line.

CO-CHAIRMAN GRAU: Let me just bring it back. The question was what factors should be considered when modeling resistance and are there other factors that should be considered, other things that should be looked at, when modeling resistance?

So, as we create this model, what would you want to include in the model that would inform you as to whether or not resistance was developing or not?

DR. GILBERT: I think the main one we got was mimic field conditions and practices.

CHAIRMAN WAGES: And that we got off.

CO-CHAIRMAN GRAU: That is how.

CHAIRMAN WAGES: A dose relationship? Dose and duration really.

DR. FEDORKA-CRAY: But what are you looking for? Are you looking for disease? Are you looking for shedding? Are you looking for carrier state?

DR. KOTARSKI: He asked us what factors we should consider, and if we are going to set up trials, one factor we have to decide is what dose we are going to look at, regardless of what outcome you are looking for. At some point you have to pick.

DR. FEDORKA-CRAY: I am talking about a challenge dose for bacteria.

DR. KOTARSKI: Oh. No. I am saying just the drug.

MR. : Are we assuming feed use here or water?

DR. MEVIUS: It could be anything.

CHAIRMAN WAGES: It doesn't matter at this point. Generic. Route.

DR. KOTARSKI: Would it be the proposed dose? In other words, are we talking -- are we at a point in the drug evaluation process in which the sponsors come forward with a dose formulation that is efficacious? They have already identified that this is the type of formulation we are thinking of; this is the efficacious dose.

CHAIRMAN WAGES: Dennis or Richard, when you go to

CVM with a drug, with an NADA, you are pretty confident of the class it is and the dose you are shooting at. So yes. It would be the proposed dose I think.

DR. KOTARSKI: If we are going to be doing a field condition, this would not be pivotal information for yes/no of drug registration. My thinking is that if we are looking at field conditions, that is an expensive study. We have gone a long way down the path for development. Dennis, I am looking at you.

If we are doing a study that has got a consequence of yes/no for the drug registration, there is a lot at stake here in terms of all of the efforts.

CHAIRMAN WAGES: Okay. In the back, please.

MR. : I am not sure I agree with the word mimic though. Maybe develop a model that correlates with field conditions. Maybe with enough information we can do a battery of studies that are much cheaper or some kind of -- even a laboratory study that is cheaper that correlates with field conditions to give the pharmaceutical company an idea of whether this compound would work in the first place before they go to the expense of running field condition studies.

CHAIRMAN WAGES: You could put them both.

MR. : I just saw something up there that said do the studies in the field, and that may not be necessary.

CHAIRMAN WAGES: Okay. But there are areas where you have got small 40x140 houses that are very small that mimic and are actually field conditions in a small experimental building. We have them at the vet school. So you could mimic or simulate. I don't have a problem with either one of those, knowing that the data idea is to try to pinpoint what we are seeing in the field as best you can.

DR. MEVIUS: I agree with you. You can mimic. Specifically for broilers. It is one of the cheapest animals to work with, so it is the easiest animal species to mimic field conditions. So that wouldn't be the main cost factor.

A very important issue was brought up by Susan Kotarski. If you would do an approval study after the development of your drug and you have a dosage regimen and residue studies, a lot of money is spent and then CVM would say, well, this is not an optimum dosage regimen with respect to resistance selection. Then you end up with a big problem.

I have been trying to make the point of dose optimization. I think you should use these kinds of studies in the development process. Include them in the development process. Of course, it depends on the category your specific drug is in and what kind of specific aspects need to be dealt with, depending on the category one or two.

So if you include it in the development process, you will have a chance of still developing an optimum dosage

regimen with respect to efficacy and also for resistance selection.

CHAIRMAN WAGES: And you think that should be required?

DR. MEVIUS: That is an approach. For me, that is the logical approach to come to control of resistance, because resistance will emerge. But what we need to do is control it so it won't be transferred to humans. We want to control it, and that can be done.

If you optimize dosage regimens and you do it in an earlier phase, then you won't have the enormous amount of development costs. So that is a potential; a possibility.

CHAIRMAN WAGES: Dennis. You had your hand up?

DR. COPELAND: No. No.

CHAIRMAN WAGES: Any other considerations for our model? Just for the resistance picture.

DR. KRUSHINSKIE: Well, bird age. Species and age type of -- I mean, if it is intended for use in two-week old date of age broilers, you certainly wouldn't want to model this in 20-week old breeders.

DR. KOTARSKI: Well, when you are doing your efficacy trials to model you have model efficacy. You are modeling that, modeling the field condition. So you are -- if you are testing for efficacy and at the same time you are monitoring for resistance emergence through a course of

therapy, automatically you pinpoint the targeted animals. Age and that type of thing. So it happens hand-in-hand.

DR. WEBER: I guess you may want to consider a factor of withdraw time as a possible incorporation. You want to see what the situation is at withdraw or --

CHAIRMAN WAGES: Does that get back to pathogen load, withdraw, or not?

DR. WEBER: It involves resistance as well.

CHAIRMAN WAGES: Okay.

(Pause.)

CHAIRMAN WAGES: Anything else? Sir?

DR. LUTHER: Dennis, I am not sure where this would fit in, but the poultry industry has practiced a shuttle of programs. Setting drugs aside or, you know, in geographical areas not using a certain drug for a while.

CHAIRMAN WAGES: That is primarily cocksidious (sic) stats and not antibiotics.

MR. : I guess I am not clear on the withdraw issue.

CHAIRMAN WAGES: I am not either, but --

MR. : Unless we are talking about basing withdraw periods on return to a baseline level, a micro flora level as opposed to residue.

DR. FEDORKA-CRAY: That would change over time though. So how do you know what to mimic and what they are

going back to? As the bird ages, --- different flora.

CHAIRMAN WAGES: Go ahead.

DR. MEVIUS: Withdraw considerations could be that you monitor what is happening during administration. But also, what the result would be at slaughter. We are talking about broilers, so it is not a very long period. And, of course, what is actually present at the time of slaughter would potentially be transferred in the food chain. That is of most interest.

So maybe that is not withdraw considerations, but those kinds of aspects need to be considered. The sampling times; when are you going to monitor. Not during administration, but look at dynamics. So, if resistance emerges. But when it is gone at slaughter, there is no problem. Yes?

DR. GILBERT: Clearly, our jurisdiction stops the minute the guy catches the bird. When you think about the drugs being applied in the animal, what happens to them after they are caught and put on the truck we don't have a lot of influence over. We have been looking at sampling times in some cases. Day 42.

DR. WEBER: But I think the reason I bring this up is the fact that some of the protocols we are looking at now do look at cessation of drug treatment and the effect on the resistance. Okay?

And one of the points that one can consider an important -- I don't know how it will factor in at some point. Perhaps like an injection type. One of the time frames is if were to find it declining, certainly that would be, I think, important information. Look at this as information in developing these studies, where the withdraw time fits in consideration of that resistance issue about withdraw the pressure.

I just throw it out for one of the issues in terms of the pressure or the dosing and decline issues that are looked at in these protocols, as well as the good doctor here showed us yesterday in the work that you were doing.

CHAIRMAN WAGES: Can I throw something out that I don't know where it fits? I just have a question. You may have the facilitator put me back on track.

Would it matter if we are looking at the potential for antibiotic resistance, transferring or at least getting into the food-borne pathogens, does it matter that the product itself -- to me it would matter whether that product was going to a plant that was going for a ready-to-cook meat in the grocery store or somebody would handle the raw product, versus it going to a fully cooked product and not be involved in any pathogens.

Is there a distinction between the potential or the use of antibiotics in poultry when they are going to be

irradiated and/or go to further processing and cooked versus something that is going to go to raw product? One has absolutely zero potential to get people sick and the other one, of course, has the bacteria potential of carrying on the carcass. Does that matter and does it fit anywhere?

DR. WEBER: Yes. You have to look at the worse case. We can't divide by two and say zero and 250,000; 125 is okay. Until we get a particular chain of events that is assured, --

CHAIRMAN WAGES: The risk of exposure --

DR. CARNIVALE: I hear CVM talking out of both sides of their mouth though.

CHAIRMAN WAGES: Risk of exposure though is included in the categorization of the drugs, and if you take the bacteria out of the equation, you take the resistance out of the equation. You take everything out of the equation. Do you not?

If you take the bacteria out of the equation, we are not talking about zoonotic potential. Well, you are laughing, but that is --

DR. MEVIUS: It is not entirely right. It was presented yesterday. If you irradiate the food products, there won't be any salmonella or camplyobacter left, but the DNA will present and transformation of naked DNA will occur and may play a role. That is not known to -- but that is not

the total answer. It was mentioned yesterday.

CHAIRMAN WAGES: Okay. Well, let's get back. I was told by the facilitator that I got off track. So let's get back and focused on what we are doing. I just wanted to get that off my chest.

DR. LATHERS: I would like to go back to a concept that Jeff added above in terms of thresholds. I think it was when we were talking about what would be done with the data. Right there. Yes. The question I would ask is are we --

CO-CHAIRMAN GRAU: Excuse me. Could we have one person talking at a time, please. Thank you.

DR. LATHERS: The question I would ask is in terms of our pre-approval studies and the results that we get from these studies, are they really independent of that threshold? Or are we going to look at the interpretation of the pre-approval study result and link these to really an established threshold or use to establish a threshold?

It is really a question of what will happen with a threshold in terms of the pre-approval study itself.

DR. KRUSHINSKIE: What is that threshold? Where is that threshold? Have you measured it? Is that the pathogen on a carcass. The pathogen in the human population?

DR. WEBER: That is the next workshop.

(Simultaneous conversation.)

CHAIRMAN WAGES: Hang on. Go ahead, Paula.

DR. FEDORKA-CRAY: I believe that the proposal or the tendency is to think that the threshold will be measured on the human side and that is post-approval. So really, that information that pre-approval studies -- I don't see how there is even a chance that they will have any impact for providing any information as far as thresholds and regulatory action.

This simply has information as to whether you are going to get a product through to even have it marketed. And the scenario I would submit to you is that regardless of what you have pre-approval, there is going to be post-approval monitoring activities. If they indicate something that was missed in the pre-approval process, that is what is going to drive having something perhaps taken off the market or having something restricted in use. Those will also influence then the threshold.

CHAIRMAN WAGES: Paula, you have to have the threshold established before you could have a mitigation, because thresholds are what we are going to by to do the mitigation or intervention strategies. Is that not correct?

DR. FEDORKA-CRAY: In theory I think that would be the nicest thing to have, but I think part of the problem is going to be where do you -- I mean, I think that the threshold is a whole other issue. It has nothing to do with pre-approval studies.

CHAIRMAN WAGES: Well, let's get on with it I guess.

DR. FEDORKA-CRAY: Right. I think the thresholds don't even need to be discussed here or anything else. I think that should be taken off, everything from there down, because it just doesn't have anything to do with pre-approval studies.

CHAIRMAN WAGES: Okay.

DR. FEDORKA-CRAY: And thresholds are totally farther down the line.

CHAIRMAN WAGES: I don't have to be the moderator of that workshop, do I?

(Laughter.)

CHAIRMAN WAGES: So we want to take the thresholds -- after PAMS, we want to take all that off?

DR. LATHERS: Well, or move it back. That is the group's thinking. I don't think you want to lose that thought.

DR. FEDORKA-CRAY: Well, I don't think it has anything -- it is not going to impact -- the pre-approval studies will have no -- will not aid in threshold or regulatory action.

DR. WEBER: Do you know that for a fact?

DR. FEDORKA-CRAY: I think, if you put it up there like that, it has a good chance that it will. I wouldn't

want anything there to be implied that hasn't -- if anything, I would put up there that this information has nothing to do with thresholds and regulatory action that may occur post-approval.

DR. WEBER: But remember, Fred mentioned that --

CHAIRMAN WAGES: Fred is not running this. Fred is not CVM.

DR. FEDORKA-CRAY: Fred is the wrong thing to say.

CHAIRMAN WAGES: You lost it when you said "Fred said."

(Simultaneous conversation.)

DR. WEBER: I think that some of the information that you may obtain in these pre-approval studies about the change of resistance with time or in a population of animals or what have you, as some of the designs have suggested, may be considered potential mitigating activities in terms of the use of the drug.

In the general sense, I could consider that potentially to be folded into regulatory actions that might be suggested as mitigations or reducing risk post-approval.

CHAIRMAN WAGES: I look at the baseline information in both the human and animal would be the one that we would observe; seeing either going together or one impacting the other, which would be the mitigation strategies, not just what we saw in pre-approval.

MS. : And not just what we see on the human side.

CHAIRMAN WAGES: One or the other. I would think they both would be.

DR. WEBER: Well, you can think that. The point is that information we get pre-approval that could help mitigate both information on prevalence or what have you and resistance information and potential mitigation strategies and only one has been suggested, or a couple, in terms of dosage and usage and things like that. It can effect perhaps one of those columns. Perhaps the prevalence information in the animal side.

But that could potentially -- as they have the potential in human drugs, potentially affect our ability to work out a regulatory strategy post-approval with producers or labeling or whatever else. I am just saying I wouldn't rule it out; of getting information that might be useful post-approval.

CHAIRMAN WAGES: You do know now that when you say something and you put those two or three words ahead of your statement, you are going to lose your credibility when you say that. Don't say "Fred said."

DR. WEBER: I won't say the "F" word anymore.

CHAIRMAN WAGES: Paula, go ahead. Then I am going to come to a consensus here on this threshold.

DR. FEDORKA-CRAY: I think that the implication that you could do a pre-approval study and have that influence in some way regulatory action post-approval is an erroneous link, because then what that would do is that would set up the scenario for having regulatory action that might be considered on something that may never occur on drugs that are already approved, because that is what you are talking about.

You are talking about drugs already approved, you are talking about drugs that are going through the approval process, and oh, if you see something here that you might interpret for another class of drugs or something, whether it has anything to do with it or not, then you are going to use that as a basis for establishing some regulatory action. There is no link there.

I think that that is -- I think it is really erroneous to have that up there. I mean, I just do. It is just --

CHAIRMAN WAGES: Okay. Let's put it to bed. Is the threshold issue -- does it need to at least stay up there for consideration as it states? Should it be taken out and not be considered in the pre-approval studies? What is the wishes? Is that the wishes? All in favor of taking the threshold portion out, raise your hand.

(Show of hands.)

CHAIRMAN WAGES: Okay. Next. All opposed?

(Show of hands.)

CHAIRMAN WAGES: You lose.

DR. WEBER: I've been there.

CHAIRMAN WAGES: Threshold will be taken out, but we did say that we would --

CO-CHAIRMAN GRAU: Reflect minority viewpoints.

CHAIRMAN WAGES: Yes. Minority versus one? That is really minority. Take it out. Okay.

Are there any other factors considered in the modeling for resistance? Let's get back on it, and we may have two questions answered before it is over. Any others?

We want to simulate field conditions; proposed dose and duration needs to be considered; route administration; species; class and age; withdraw considerations as it relates to resistance specifically and the sampling. I thought we just had sampling time, i.e., slaughter, et cetera. It may be slaughter, but it may not be. Is that right?

(No response.)

CHAIRMAN WAGES: Are there any other factors that we should consider for a model in looking for resistance?

DR. MEVIUS: Maybe here we are talking about the animal trial, but still, in vitro information on resistance. Transfer of resistance.

CHAIRMAN WAGES: The mechanism.

DR. MEVIUS: Mechanism of resistance should be included in the model or done before the model. And whether that is really predictive for the field situation can be studied in the model. With a lot of antibiotics the mechanisms are known. For new antibiotics it would be nice to have information on the mechanism and whether in vitro transfer of resistance occurs where so there is evidence of plasmid mediated. Something like that.

CHAIRMAN WAGES: So mechanism of resistance or in vitro testing?

DR. MEVIUS: In vitro testing, mechanism of resistance, transfer of resistance, transfer rate; those kinds of things. Yes.

CHAIRMAN WAGES: Okay.

(Pause.)

DR. FEDORKA-CRAY: I have a problem, Dick, with including transfer rate as a pre-approval condition, because we know so little about -- I have a big problem with that in general because we know so little about that. We don't have a very good idea about the conditions that cause that.

I mean, all of this talk about naked DNA dancing around and everything. We have so much naked DNA around here all the time that it is hard to believe that we are not seeing more resistance than we have. I think that we are backing ourselves into a corner of trying to ask for

information that we don't have a means for even beginning to describe. You know, it isn't like saying let's do testing for camplyobacter or salmonella or something.

DR. MEVIUS: Right. But maybe the general concepts, whether -- the mechanism of resistance, whether it is chromosomal or plasmid mediated.

DR. FEDORKA-CRAY: I think that is great. That would be informative. I wouldn't mind putting like some qualifiers or special considerations at the bottom where you could say that you would look for transfer of resistance. You know, studies should be conducted in a research setting to define the transfer of resistance or something along those lines; so that those would come later, but not as a part of the pre-approval process.

DR. MEVIUS: Right.

DR. FEDORKA-CRAY: I mean, you could spend years on --

DR. MEVIUS: I agree. Yes.

CHAIRMAN WAGES: Then it is irrelevant. Right?

DR. FEDORKA-CRAY: It is irrelevant.

CHAIRMAN WAGES: So we don't need it on there.

DR. MEVIUS: No. If it is there, if we know it, it is important.

DR. FEDORKA-CRAY: It is irrelevant for a pre-approval process. It is not irrelevant for --

CHAIRMAN WAGES: See, I don't think it is, but maybe I -- I don't think it is irrelevant for pre-approval.

DR. KOTARSKI: To give you an example, fluoroquinolone resistance is -- the most fluoroquinolone resistance that we have seen it is mediated by mutation. Okay? There is one report of plasmid mediated fluoroquinolone resistance. It is not well characterized, and the report occurs after many years of fluoroquinolone use in human therapy.

So that is important information; to know that the predominant mode of fluoroquinolone resistance comes from the chromosome. It doesn't seem to be transferred that frequently. That is important information to know generally about the compound.

Now, there are other classes of compounds or whatever that have plasmids that transfer the resistance. For example, the vancomycin resistance.

CHAIRMAN WAGES: I think it is important.

DR. LUTHER: Was that knowledge learned prior to approval? Or how was that knowledge acquired?

CHAIRMAN WAGES: Well, if you are talking the Israeli study on the plasmid, that was last year.

DR. KOTARSKI: George Jacobi's work.

CHAIRMAN WAGES: Yes. That was post-approval.

DR. WEBER: I think it is very important

information, because I think it is -- it goes with what the nature of the resistance is in the animal, to be contrasted with, later on, if you can identify the nature of the resistance in people.

If there is juncture there, I mean, you have to assume Sam's knowledge. You know, that it is identical to resistance that is generated in animals. So I think it is important to have some knowledge about the resistance as you find it.

CHAIRMAN WAGES: I agree. But is it --

DR. WEBER: Good.

CHAIRMAN WAGES: Is it necessary for a pre-approval study to have that? That is the question.

DR. WEBER: Good baseline information. I believe it is.

CHAIRMAN WAGES: Okay.

DR. KRUSHINSKIE: Can I make a housekeeping point? I guess I am being confused with the first six items. They are talking about a specific animal model. I guess is where we have kind of evolved here. We are looking at field conditions, proposed dose, route, administration, et cetera. And then this last one is information that is probably important to know, but it is not really part -- to me, that is another topic.

One is an animal model, if we are going to do an

animal model, and what is our objective of this animal model? We listed withdraw considerations and sampling time, but what is it that we are trying to do here? What is the overriding objective?

Is it to measure resistance in those populations that we addressed, we listed initially, before and after treatment? Is that what we are trying to -- now we are trying to put together a model that does that? I think we are putting the cart in front of the horse here and we are mixing apples with oranges.

CHAIRMAN WAGES: That is probably a good point.

DR. MEVIUS: I don't quite agree. I think trying to do an animal study to understand what you see in animal study would be very good information, whether it is chromosomal or it is -- whether resistance is linked to other antibiotics.

We saw in my kind of studies that a lot of factors effect resistance. So it would add to the understanding. So I would think that it is important to know prior to start such an animal study. You don't have to do all. Like Paula said you can work on, for years, all the different resistant genes that can be present. You don't have to define them all because that is really scientific work for a CDC-like group. But at least know the general concepts of resistance that makes you understand better what is going on.

MS. : That can be a literature review basically of existing knowledge.

DR. MEVIUS: Yes. Sure. Of a new drug it should be something else.

CHAIRMAN WAGES: Dennis?

DR. COPELAND: That is what I was going to ask. And I don't know. I am asking the question. If you have a brand new compounds, a brand new class where you don't have literature to rely on, is this a big burden to do this?

DR. WEBER: Ask the guy. There is one sitting right here. He can tell you how long it takes to fingerprint a plasmid.

MR. : (Away from microphone.) I would suspect that you are going to have a pretty good idea based on the class, which is what I think all this started with.

MR. : My question is if we had a brand new class.

MR. : It shouldn't be that. It is not that difficult to clone. In fact, if you are looking at cloning in general, it is one of the easiest genes to clone because the selection is pretty ---

DR. KOTARSKI: You could take a set of isogeneic strains. In other words, a number of different strains, different known resistance determinants. Take your new drug if you want to get cross-resistance in those organisms that

have a known resistance determinant.

(Simultaneous conversation.)

CHAIRMAN WAGES: Okay. In our modeling we want to at least have an idea of the mechanism of resistance. All right. Let's go.

MS. : In this model, which organism are we going to select as a challenge here? Do we select all salmonella, camplyobacter, E. coli. or -- you know, we should select which organism we select as a challenge study here. Say from one to seven or whatever.

MS. : Do we need a challenge organism?

CHAIRMAN WAGES: You don't need a challenge organism for --

MS. : How do you monitor it then? As you indicated ---

CHAIRMAN WAGES: Pardon me?

MS. : Which organism as an indicator develops resistance then?

DR. MEVIUS: We have got to monitor resistant in the commensal flora. There is no challenge organism. You look at normal flora in the animals and see what the effect is.

DR. GILBERT: For transfer can we insert --

DR. FEDORKA-CRAY: Transfer is not an issue.

DR. WEBER: It is not an issue?

DR. FEDORKA-CRAY: Transfer is not an issue here.

DR. WEBER: It is at some point. Whether it is right here, that is the next step.

CHAIRMAN WAGES: Are you saying that if we are looking at resistance in a target bacteria we are trying to treat?

MS. : Yes.

CHAIRMAN WAGES: There would need to be a challenge of that organism?

MS. : Yes. Then you can look at it and develop a resistance. Right? So if we don't challenge the organisms we know, how do we look at resistance development?

DR. KOTARSKI: When you use a challenge organism, are you mimicking field conditions? Are those working at two different purposes?

CHAIRMAN WAGES: If you are simulating field conditions and/or -- I won't say in vitro, but in vivo in a small -- you are going to have to challenge. You are not going to be able to mimic. In a small environmental house you could mimic the conditions without a challenge, such as -- I don't know the answer to that.

DR. KRUSHINSKIE: What --- pathogens? What if they are not present?

CHAIRMAN WAGES: They are not in our house. Well, they are not. They are not there. I'm sorry, but they are

just not. Go ahead.

DR. MEVIUS: You could challenge in such different ways different amounts or organisms. That would a lot of variables. I would suggest again to look at the bacteria that are present in the animals and look at the effect on the present.

Whether that is a direct relation with zoonotic bacteria, that is a different question. Look at these commensal on the gut flora in the animals. If you are going to challenge them and then look for resistance selection, that will be very difficult.

MS. : What about the nature of -- the particular study that contain salmonella or camplyobacter, but are now -- you know, maybe the real situation --- so how can you correlate your model in the field; real life?

DR. KRUSHINSKIE: Can you correlate the development resistance in one species to development resistance in another? You can't. You can't say, if it develops an enterococcus, that it is going to develop in E. coli. and camplyobacter, because it doesn't work that way.

DR. MEVIUS: That is not exactly correct. Transferrable resistance between species is a very common phenomenon and also between gram positives and gram negatives.

DR. KRUSHINSKIE: We have higher resistance levels

to camplyobacter and fluoroquinolones than we do for E. coli.

DR. MEVIUS: That is very correct. Camplyobacter is a very different species regarding fluoroquinolones than E. coli. That is true. That is a problem.

CHAIRMAN WAGES: Okay. So we have got a monkey wrench thrown in here with this challenge organism, and we need to deal with it or dispel it. One of the two.

DR. KOTARSKI: Maybe I am thinking of the study naively. But if I go into your house and you say, well, I don't see any salmonella. Okay. You don't have any salmonella. But I am coming to you and I have an idea of a dose I want to use and the point I want to refine that dose. Okay?

And I say, I want to contract with you a small study to get a better refinement of my dose, and as I refine my dose, I want to have some information as well about changes in resistance determinants. Now, I can't measure all the commensal bacteria, but I know that this drug has activity against E. coli and it isn't very active against enterococci.

So I want to know if the populations of E. coli change in their resistance during the course of therapy for whatever this disease is. Now, the question is to look at that disease. If I have to have a challenge organism to get that disease to happen, I will ask. If, in the process of

treatment in that challenge organism I get resistance, does that occur? Do I have changes in resistance for sensitive populations of E. coli that are present in the animal? Maybe another organism. I can't do salmonella. I just can't. But at least I have got two organisms I looked at.

I looked at my target pathogen, I did a study and I can characterize, during one course of therapy, whether or not there were changes, period. That is what I am thinking, but maybe that is naive.

MR. : So what does that tell you as far as impact on zoonotic organisms, if that is our goal?

CHAIRMAN WAGES: Whoever. Yes.

DR. WEBER: Didn't we deal with that in the first hour, that we are going to look at target organisms and four or five other known organisms? Those are all up for grabs to look at this as the potential impact of that, and they covered the major classes and major pathogens of concern.

If that is what the challenge is to those four or five bugs, then isn't that issue? Are you just going to culture a plate with a certain level of this disease -- of this antibiotic on it and swab it with critical material and see what happens?

MR. : I think the problem is, if you want to do this under simulated use conditions, then you are relying on the commensal organisms that are in the bird, which may or

may not include the ones -- the zoonotic ones that you are interested in. That is the problem.

DR. MEVIUS: Well, for broilers the nice thing -- when there are positive camplyobacters, all animals are shedding them at high levels. So camplyobacter can very well be present before you start. You can test for them or you can select animal populations to be positive for camplyobacter. Then you can also use camplyobacter as being present, because challenging them you would add a lot of -- well, it wouldn't mimic the field situation.

CHAIRMAN WAGES: Right. Salmonella is intermittent shedders, and we have all sorts of problems with them.

MS. : Well, you could put cedar birds in these houses too. If you had separate models, you don't have a separate trial for each bug of interest.

CHAIRMAN WAGES: Does this challenge organism need to stay up there? Or did we actually take care of it back where we had our bacteria listed?

DR. KOTARSKI: You can put field study may include challenge -- target pathogen you said?

CHAIRMAN WAGES: Field studies may mimic field --

DR. KOTARSKI: Instead of deleting challenge organism entirely, based on your point, to say mimicking field conditions, and we put in parenthesis "may include a challenge target organism." No?

DR. MEVIUS: Do you understand what she means?

CHAIRMAN WAGES: No.

DR. MEVIUS: For instance, if postelmotisity (sic) is the target organism, which may be not the case, then you challenge them with pasterella (sic), then you look at what is happening at the target organism, but also study the effect of this dosage on E. coli. and camplyobacter if they are present. So that is the suggestion.

CHAIRMAN WAGES: I understand that. Thank you. Does that reflect what we are dealing with here?

DR. FEDORKA-CRAY: Take out eight and move it up to one then.

DR. MEVIUS: Maybe. Yes.

CHAIRMAN WAGES: Okay. Copy it and paste it.

(Pause.)

CHAIRMAN WAGES: Okay. While he is doing that, any other factors to consider?

(No response.)

CHAIRMAN WAGES: Do we want to review these again?

DR. MEVIUS: Maybe. Yes.

CHAIRMAN WAGES: Okay. Let's just go through them. Field studies may utilize the challenge organism to better stimulate field conditions.

DR. KOTARSKI: Challenge target organism.

CHAIRMAN WAGES: Challenge target. Okay. Dennis?

DR. COPELAND: You need to clarify if you are talking about true field studies in commercial operations --

CHAIRMAN WAGES: You are not going to challenge.

DR. COPELAND: You can't challenge. If it is a simulated field condition, like you have number two, that is a different story.

CHAIRMAN WAGES: I buy that. Good point.

DR. KOTARSKI: I am confused. There was one point when we discussed the concept that we don't want to be doing resistance emergence characterization when we are the final dose formulation. We are refining our dose of the challenge organism. This is in a smaller study. You can have studies where we -- you know, we do small studies. Field conditions implies to me a large study.

CHAIRMAN WAGES: Not necessarily.

DR. MEVIUS: In broilers a large study can be small. Broilers are small animals. They are only -- the processing period is only a couple of weeks. So it is not as big as using large groups of cattle or pigs.

DR. KRUSHINSKIE: I think of it as a colony house situation with litter, versus a pen trial or battery or something like that.

DR. MEVIUS: Not 30,000 animals.

DR. KRUSHINSKIE: I still have a problem with number eight. I don't k now that you want those studies on

the mechanism of resistance to be --

CHAIRMAN WAGES: That is fine. I want to go through them all again, and we will nail that when we get to it. Are we now better understanding the field studies? And I am like Beth. We could have 500 birds. Or, in our house, we could have 8,000 in a field situation on litter that is not a true commercial situation. So, we are comfortable with one?

DR. FEDORKA-CRAY: Add target after challenge.

CHAIRMAN WAGES: Add target after challenge. May utilize a target challenge organism? Or challenge target.

MS. : Target pathogen.

CHAIRMAN WAGES: Okay. I will be talking, so it won't matter. Yes?

MR. : Number one starts with number two. Simulated field conditions (away from microphone.)

CHAIRMAN WAGES: Jeff, put a period and then put "these may" and take out number two. Is that what you are saying?

MR. : I would start number one with what is in number two. Yes.

(Simultaneous conversation.)

DR. GILBERT: Okay. And then take out number two?

CHAIRMAN WAGES: Yes. And then --

DR. MEVIUS: And then, between records, to better

stimulate disease conditions.

CHAIRMAN WAGES: Yes. We are redundant here. We have got field conditions twice.

DR. MEVIUS: Yes. But the suggestion was in the second time you are using a challenge for the target pathogen to simulate the disease condition, which are also maybe the field conditions, but --

CHAIRMAN WAGES: How about field/disease condition?

DR. MEVIUS: Very good.

CHAIRMAN WAGES: Okay. Proposed dose and duration. Are you comfortable with that? Why have we got an asterisk behind that?

DR. GILBERT: I had it linked down to the optimum dose for resistance considerations and effectiveness. Do we need all that? Or just leave it at --

CHAIRMAN WAGES: I would just put proposed dose and duration. Do you want to emphasize -- maybe we ought to put that back up with two. This optimum dose for consideration and effectiveness, somebody commented that they wanted that tagged with two. I don't know if it was one person or 100.

MR. : It fits there.

DR. GILBERT: Should the proposed dose be the optimum dose for resistance considerations and effectiveness was sort of the tenor.

CHAIRMAN WAGES: Dennis, you have your hand up.

DR. COPELAND: I just want to make sure we are all clear on the same thing here. These are simulated field conditions where we are going to challenge the birds with a target pathogen. So say the drug is proposed for use against E. coli bacillosis. You are going to challenge it with E. coli.

So we are going to look at that and we are going to look at changes in susceptibility to E. coli, but we are also going to look at zoonotic pathogens. Right? And we discussed that probably could easily be done for camplyobacter. But for salmonella, there is no assurance if salmonella is going to be there.

CHAIRMAN WAGES: Correct.

DR. COPELAND: Okay. So we are just going to forget about salmonella?

DR. FEDORKA-CRAY: No. It may be there some time. It may not be there other times.

MR. : But how many studies are we going to do?

(Simultaneous conversation.)

CHAIRMAN WAGES: Is the focus going to be -- I thought the focus was still going to be the target organism, but if we can measure commensals or the zoonotics and their presence, we would.

(Simultaneous conversation.)

MR. : There is no assurance that the target organism is going to tell you anything about the zoonotic organism and how they react to the drug.

CHAIRMAN WAGES: They could care less whether the drug works or not of course. That is a good point.

DR. KRUSHINSKIE: Why can't we challenge it with the food-borne pathogens? Because the commensals are present. You can put cedar birds in for salmonella, and instead of putting in E. coli, whatever the target pathogen is, that is one study.

(Simultaneous conversation.)

MR. : You could put the cedar birds in first for salmonella, and then you can come back and challenge them with E. coli.

CHAIRMAN WAGES: You wouldn't have to do that.

DR. FEDORKA-CRAY: I would just put out -- you could put some cedar birds with salmonella and you could put some cedar birds with camplyobacter too, for that matter. The only problem is I wouldn't introduce camplyobacter until the natural -- and you don't have to do that, because campy is going to show up by three weeks anyhow.

So I wouldn't even bother with campy, but you could put a cedar bird with salmonella in there quite easily and see what happens to it.

CHAIRMAN WAGES: Which salmonella are we going to

use?

DR. FEDORKA-CRAY: Now, that is a better question, and I think that gets -- you know, you are -- because you can pick one that won't be very resistant, no matter what you do, and you can pick one that will suck up everything.

DR. KRUSHINSKIE: You also have some that are more invasive than others. I am not sure if that makes a difference on re-culturing it again.

DR. FEDORKA-CRAY: No. I don't -- that adds a surveillance question, as opposed to a resistance question. You know what? I guess, to avoid all of this though, what I would probably do is I would go out and I would make sure I had a house that I knew had salmonella.

I mean, when we test things, when we test in the field, if we want to find -- like if we want to look at -- for instance, right now we are looking at the impact of antimicrobial use patterns on swine farms. Okay? Well, we wouldn't select a farm until we went in and we knew that we were going to have salmonella there. All right?

Okay. If you wanted to do something -- like you have these small housing units or something, you could go to a swine -- I mean, if you go to a poultry farm and, if nothing else, you can take some litter from another poultry farm with those representative serotypes in it and put that down in your --

DR. KRUSHINSKIE: That adds a whole lot of variability of unknown of what you are putting in that house.

DR. FEDORKA-CRAY: That adds less variability than trying to pick some serotypes, because you are going to be criticized for not looking at the right serotype.

CHAIRMAN WAGES: What are the two top isolations of human salmonellosis? Hydleberg?

DR. FEDORKA-CRAY: Yes. Usually the top three are Tithemerium, Hydleberg, enteritidis.

DR. MEVIUS: It is a model study. So, as a model, you could choose tithemerium.

CHAIRMAN WAGES: That would give us something that would be relevant in humans.

(Simultaneous conversation.)

DR. FEDORKA-CRAY: Do you use a Copenhagen?

CHAIRMAN WAGES: Most of it is Copenhagen.

DR. FEDORKA-CRAY: I would say that is not true.

CHAIRMAN WAGES: It is in poultry.

DR. FEDORKA-CRAY: No, it is not. Not when we are getting at slaughter, Dennis. And I just gave those sheets away, or I would be able to tell you. He has got the list. I have list of the last three years of what the serotypes are for poultry.

DR. KOTARSKI: If we add salmonella purposely in these studies, do we compromise our objective to understand

efficacy? Because we are trying to optimize dose for efficacy and we are trying to minimize resistance or give some characterization of resistance in commensals.

But if you add a dimension of saying it has to have salmonella in it, then do you compromise your efficacy component?

DR. FEDORKA-CRAY: This is where you are going to have to seriously ask yourself do you really need pre-approval studies.

DR. WEBER: You have to optimize your dose first for efficacy. Then you throw in the bug that she says is an appropriate. Then you are going to look then at these studies for the development of resistance.

DR. FEDORKA-CRAY: How many studies are you going to do then?

DR. WEBER: You tell me. Give us your best shot, you know, in terms of --

DR. FEDORKA-CRAY: Zero. I am not saying that there isn't one that we couldn't use. The question is it going to -- what are you going to do with the information? I mean, you have to know what you are going to do with the information? And what are you going to do with the information?

If you put tithemurium in there and you get all kind of resistance out of it and then they are going to say,

no, you can't use it because this makes us nervous or we get an unacceptable level, then are you going to go back and your boss is going to say, you should have used puna, and you are out.

DR. WEBER: We can't use one that is resistant to resistance development. And I don't know your bug.

DR. FEDORKA-CRAY: Right. I can appreciate that. But again, you are putting them in situations that may be aberrant that may not necessarily reflect -- be a true reflection and be fair to give you a fair analysis. You don't want to get caught on the other side of being criticized for being unreasonable either.

DR. WEBER: Never happen.

CHAIRMAN WAGES: Maybe tomorrow morning for an hour we will take do we need pre-approval studies as a focused question, and maybe our first comment in the afternoon may be to answer that question.

DR. MEVIUS: Talking about salmonella, a lot of problems are coming up, and it seems to be a lot like the pathogen load studies. You can do it in a lot of ways, and you can come to different conclusions. So maybe salmonella is not a model bacteria in this kind of model to use.

We should better focus in the bacteria that are present in small numbers, because that is the actual situation. You can work with them and you can do, more or

less, a reliable study. With salmonella there is so many choices you will make and Paula is telling us it is not reliable, what you will get out of it. So you can't do anything with it.

CHAIRMAN WAGES: Richard?

DR. CARNIVALE: Is looking at resistance in commensal bacteria or in E. coli or in other bacteria that aren't considering food-borne pathogens relevant to the question? That is where you always fall down. If you are looking at global health concerns, --

DR. MEVIUS: Right.

DR. CARNIVALE: -- then, yes, you could look at resistance. I agree. You could measure resistance a lot easier in E. coli. But then you have to say is it relevant to public health, and that is where the disconnect occurs.

CHAIRMAN WAGES: And that should be the focus to answer the question of public health, and that is why we are here. Paula?

DR. FEDORKA-CRAY: Dik, I think we are going to run into another problem too with camplyobacter because we know now, from of the studies that we are doing, you know, from our slaughter what we are getting. We are getting almost 30 percent campy coli out as opposed to campy jejuni, and we know that even within our jejuni population -- I mean, it has been well documented in the literature that even on the same

poultry farm you may have up to five different strains of jejuni on the same bird.

And we know that within those five different strains, what we get out from samples, that they may have different resistance patterns. So how many isolates of campy do we pick? Do we pick jejuni? Do you look early? Do you look late?

DR. WEBER: I agree. It is present, but it is not one camplyobacter.

DR. FEDORKA-CRAY: It is not one camplyobacter.

(Simultaneous conversation.)

CO-CHAIRMAN GRAU: Can we reflect anything up here? That could also reflect the conversation, which is it is complicated and there are things that are not resolved and unknown. What could we say up here that could summarize the multiple conversations that we have heard so that the world could know about it tomorrow?

DR. FEDORKA-CRAY: I think that this is a really good exercise to put out to show the complexity of the issue, because I don't think that people start to realize all of the permutations that go until you start to put it down and say, all right, now what are you going to do. Okay?

I think if anything -- in my mind, what could be summed up from this is this is the complexities and frustrations associated with trying to develop a model which

will adequately address a public health concern, because of the complexity issue.

The next part would be do we need to begin to think outside of the box regarding impact of human health from these types of studies? You know, is this going to adequately address the problem? Quite frankly, from what we have just said, the answer is no.

MS. : How much useful information is going to come out of this in terms of being relevant?

DR. FEDORKA-CRAY: Enough to keep most of us in a jar, but --

MR. : I think you need to capture the difficulty with salmonella and camplyobacter.

CHAIRMAN WAGES: Okay. Get it up here so I can do that. Give me some bullet points that I can say, look, we talked about simulating field situations and we looked at trying to make that relevant to food-borne pathogens in that field situation. Here were problems. That is what I have to tell them tomorrow.

DR. FEDORKA-CRAY: Okay. So the first thing would be like lack -- I don't want to say inadequate supply of salmonella.

DR. WEBER: Yeah. Right.

DR. FEDORKA-CRAY: You guys don't believe anything.

CHAIRMAN WAGES: Salmonella is lack of positive

houses consistent.

(Simultaneous conversation.)

CHAIRMAN WAGES: Low incidence and inconsistence of salmonella. We have trouble finding positive salmonella chickens on the broiler side. The other thing would be campy is multiple species.

DR. FEDORKA-CRAY: Serotype issues. For both of those.

CHAIRMAN WAGES: For both of them.

DR. FEDORKA-CRAY: For both.

MR. : Is there a serotype issue on the human side as well?

CHAIRMAN WAGES: That is what I was getting to with Copenhagen and Hydleberg. That is what I thought were the primary isolates coming from sick people. So that is what I was going by. It wasn't from chickens.

DR. FEDORKA-CRAY: And that is true for humans.

DR. GILBERT: Anything else?

DR. FEDORKA-CRAY: You can just put culture -- isolation culture methodologies; isolating problems.

DR. MEVIUS: Yes. That is important

CHAIRMAN WAGES: We need a PCR form.

DR. FEDORKA-CRAY: No. No.

CHAIRMAN WAGES: Excuse me. Retract that from the record.

DR. KOTARSKI: There was some discussion to -- because of the low incidence of salmonella, we discussed a salmonella challenge, and we said if we had -- we picked salmonella infected birds, but that compromised our objective to address effective dose.

CHAIRMAN WAGES: Yes. By simulation, simulating the field and challenging with a food-borne pathogen we could compromise that.

DR. KRUSHINSKIE: We also had very low levels of resistance factors.

MR. : Dennis, when we get through with this issue on the organisms, I think there is another factor that we haven't looked at.

CHAIRMAN WAGES: Okay. Let's get through this and then we will --

DR. GILBERT: What was that, Paula?

DR. FEDORKA-CRAY: Phage types.

(Pause.)

CHAIRMAN WAGES: Okay. So that captures the essence of me explaining the potential problems.

DR. FEDORKA-CRAY: You could probably add one more and that would be challenge dose. Now what do you challenge? How do you challenge the house? Depending on how you challenge them, that would effect outcome.

DR. LUTHER: Let me ask a question. It just seems

to me that the traditional effectiveness studies should be independent of this study that addresses the public health concern. Am I off base on that?

CHAIRMAN WAGES: Say that again.

MR. : That is what I was going to bring up. I mean, I am not sure for resistance, but for efficacy we need to replicate, and that is important because it makes your study a lot bigger and more labor intensive. And again, I don't know how that impacts the resistance issue.

But certainly, if we are looking at efficacy here, we are going to have to replicate each treatment regiment probably six to eight times in order to generate -- the pen is going to be the unit of measurement, and so we have to have enough numbers to show a statistical result.

CHAIRMAN WAGES: Wouldn't you do the same thing with resistance?

MR. : I would think so. I would think you need replication for that as well.

CHAIRMAN WAGES: Would that be important? We need to go up again and put -- and that is almost like validation. Right? Put number eight somewhere in there. Put replication/validation. That is a good point.

DR. LUTHER: I think Susan was asking the question of whether the efficacy part is compromised when you put cedar birds in and that sort of thing, and I think the answer

is yes. So I see these as separate studies.

CHAIRMAN WAGES: You mean efficacy versus the resistance. I agree with that. I think we agree with that. I think the efficacy issue came into if we challenge, if we do this, does it effect our efficacy. No? What?

DR. CARNIVALE: What I was thinking is does one capture that?

CHAIRMAN WAGES: Maybe.

DR. KOTARSKI: Before you find the dose, do you look at a couple of different doses and then evaluate resistance? Do you maximize resistance first? Look at resistance and then do your -- the efficacy study?

CHAIRMAN WAGES: To me you have to do your efficacy study and then determine, after that, what impact your efficacy dose has on resistance.

DR. KOTARSKI: So this is going to be my efficacy. I haven't looked at resistance. I said impact on resistance emergence in the past. I have identified my efficacy. That is what I am going with. I am not going to look at resistance. If I get resistance emergence, I have already done the efficacy study. So I am not going to change. Or are you going to do a couple of different doses with resistance emergence?

CHAIRMAN WAGES: That is up to the company. If I found the resistance based on my dosage, then I may, as a

sponsor, go back and say, well, could I increase it, decrease it?

DR. KOTARSKI: It is scary because --

CHAIRMAN WAGES: Don't get scared. Don't be scared. Trust me. I am a doctor.

DR. WEBER: I think someone suggested that some of these studies will be going in parallel and you will have some indication of efficacy from pilot work as you are going into the field, and some of these things can begin then as well. Or you could bracket the anticipated doses. You could have a second dose if you think -- so you go on a parallel track with perhaps bracketing some potential doses.

DR. KOTARSKI: I think I will do a pilot study.

CHAIRMAN WAGES: Go ahead.

MR. : Just to clarify one thing. So we are talking about changing our entire philosophy on how we select our data? I just want to make sure we are all aware of that, because right we look at efficacy and we have always been told not to put anymore drug out there than the efficacious dose.

And we are going to take that and we are look at the resistance and now we may increase the dose based on -- if you look at optimize for resistance considerations, are you going to increase that dose based on resistance considerations? And then, after you do that, are you going

to look at target animal safety where you had efficacy and your target animal safety was fine, but if you increase the dose for resistance considerations, your target animal safety falls out. I am just asking.

CHAIRMAN WAGES: That is the problem with this whole situation, but that is the reality. I think Tom said what this is going to entangle is the domino effect on the drug discovery process when you are looking at it -- because that is exactly what I think you would have to look at, is we are going to dose it. Does it treat it? Yes. Okay. Does that dose minimize resistance? Yes or no, maybe; whatever.

And then you are going to have to go make a decision. Do we increase that dose and what effect does that have on withdraw safety, toxicity, the whole -- that is exactly what this does.

MR. : You are suggesting though that this (away from mike.) I think that the increase in resistance, if it is observed, needs to be taken into consideration ---

MS. : But how much increase in resistance and in what? If you use it, it is going to increase resistance somewhere along the line. So what are you going to say? Any increase?

CHAIRMAN WAGES: Well, we are talking about looking at resistance in humans, not the animals.

DR. WEBER: I don't know to what extent you use it,

but I think one needs to consider the pharmacodynamic information that you would be gathering as you go, the time above MIC. So you might effect the resistance. And those are the sort of things you could be looking at early on in terms of your micro-people, whether or not you are going to hop on it five hours and just once a day as opposed to all day along above the MIC, which might increase the potential for resistance.

Some of those early issues about resistance mechanisms and development, I think your micro people are going to understand this a lot better than waiting until we are down to try to decide what to take into the field. They need to factor these things in in deciding the dose up front.

DR. KOTARSKI: And if you are talking about drug exposure --- then another aspect that doesn't come into the drug development process right now, and I would challenge people to look in their -- is the drug concentration in people. Most chemists don't do that very often.

So, to do what you are talking about in terms of optimizing those ratios of drug to bug, that is another -- that is a mystery.

CHAIRMAN WAGES: Okay. We are getting down to the nitty-gritty. Dennis, that problem, was that addressed with the efficacy?

DR. COPELAND: Yes. Mine was the replication.

CHAIRMAN WAGES: Okay. Is there any concerns with -- we will probably come in tomorrow and redo this, number eight. Think about it; sleep on it. I will be studying it, and then we will start with another question tomorrow.

The questions I think we have kind of got a handle on so far is what pathogens should be focused on pre-approval studies and how much they be selective, and I think we have covered that. And should surrogate organisms be used, and we have talked about commensals, E. coli, gram negatives, et cetera.

What factors should be considered when modeling resistance development and pathogen load changes? We have done the pathogen load. We are now talking about the considerations. The other ones we have left are what role could the various types of data play in evaluating microbial effects and what is that data that we want to collect.

I think we could probably then go down to number five. "Are there other alternative approaches or concepts that we ought to consider?" And then, what are the positive aspects of this model that we have basically created.

CO-CHAIRMAN GRAU: And what are the limitations and can the approach predict resistance development.

CHAIRMAN WAGES: Yes. And what are the limitations to what we have proposed and can it predict resistance. So we have got --

CO-CHAIRMAN GRAU: Or how could it.

CHAIRMAN WAGES: How could it? What are the mechanisms involved in it. So we have got a couple of biggies left. I want to thank you all very much.

CO-CHAIRMAN GRAU: 8:30 tomorrow.

CHAIRMAN WAGES: At 8:30 we will be here to start. We are going to start at 8:30 with or without you.

CO-CHAIRMAN GRAU: Hopefully with you.

(Whereupon, at 5:21 p.m., the meeting was recessed, to reconvene February 24, 2000, at 8:30 a.m.)